CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125160/S-080
(originally approved as BLA 125271)

Trade Name: **CIMZIA**

Generic Name: **Certolizumab Pegol**

Sponsor: **UCB Inc.**

Approval Date: 05/13/09

Indications: Treatment of adults with moderately to severely active rheumatoid arthritis.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125271/0

BLA APPROVAL

UCB, Inc.
1950 Lake Park Drive
Smyrna, GA 30080

Attention: Sandra Bonsall, RAC
Associate Director, Regulatory Affairs

Dear Ms. Bonsall:

Please refer to your biologics license application (BLA) dated November 29, 2007, received December 6, 2007, submitted under section 351 of the Public Health Service Act for CIMZIA® (certolizumab pegol).

We acknowledge receipt of your submissions dated February 15, March 14, April 3, May 16 and 30, July 18, August 11, 12, 14, 20, 25, and 28, September 3, 9, 10 15, and 30, October 14 and 21, November 21, and December 12, 18, 19 22, and 24, 2008, January 15, March 12, and April 21, 2009.

Your March 12, 2009, submission constituted a complete response our January 2, 2009 action letter.

We have completed our review of this application, as amended, and your biologics license application for CIMZIA® (certolizumab pegol) is approved. You are hereby authorized to introduce or deliver for introduction into interstate commerce, CIMZIA® under your existing Department of Health and Human Services U.S. License No. 1736. CIMZIA® is indicated for treatment of rheumatoid arthritis.

Your application for CIMZIA® was not referred to an FDA advisory committee because your product is a member of the class of tumor necrosis factor (TNF)-blockers and the safety and efficacy data did not pose unique concerns beyond those applicable to other biologic products approved for the treatment of rheumatoid arthritis.

Under this license, you are approved to manufacture certolizumab pegol drug substance at (b) (4). The final formulated product will be manufactured, filled, labeled, and packaged at (b) (4) and at (b) (4). You may label your product with the proprietary name CIMZIA® and will market it in 200 mg/mL sterile solution in pre-filled syringes.

The dating period for CIMZIA® shall be 18 months from the date of manufacture when stored at 2 to 8 °C. The date of manufacture shall be defined as the date of (b) (4) of the formulated drug product. The dating period for your bulk drug substance shall be (b) (4) We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of CIMZIA® to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical to the enclosed labeling and Medication Guide. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved STN BL 125271/0**".

Pursuant to 21 CFR 201.57(c)(18) and 201.80(f)(2), patient labeling must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the labels submitted on July 18, 2008, as soon as they are available but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved STN BL 125271/0**". Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to < 2 years because necessary studies are impossible or highly impracticable. This is because JIA polyarticular subtype most often occurs in children age ≥ 2 years and older and is infrequent is children aged 0 to < 2 years of age.

We are deferring submission of your pediatric studies for ages ≥ 2 to < 17 years for this application because this product is ready for approval for use in adults and pediatric studies have not been completed.

Your deferred pediatric study required under section 505B(a) of the FDCA is a required postmarketing study. The status of this post-marketing study must be reported annually according to 21 CFR 301.70 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

1. Assessment of pharmacokinetic (PK/PD) parameters and dosing, safety, tolerance and immunogenicity in the pediatric population ≥ 2 years to < 17 years with polyarticular JIA. The adult RA exposure-response should form the basis for these dose simulations in pediatric patients.

Protocol Submission:	October 2009
Study Start Date:	December 2010
Final Report Submission:	October 2015

Submit final study reports to your BLA 125160. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated **"Required Pediatric Assessment."**

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the following long-term serious risks in adult patients with RA with the use of CIMZIA (certolizumab pegol): (1) cardiovascular and thromboembolic events, including congestive heart failure, hypertension, transient ischemic attack (TIA), stroke, tachyarrhthmia, atrial fibrillation, venous thrombosis and associated phlebitis; (2) serious infections including opportunistic infections, and (3) malignancies, both solid tumors and lymphomas.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following postmarketing clinical study:

1. A postmarketing clinical study registry in adult patients with moderately to severely active RA that would assess the longer term risks of serious infections, malignancies that have been reported with TNFα blocker therapy as well as the longer term risk for cardiovascular and thromboembolic events, including congestive heart failure, hypertension, TIA, stroke, tachyarrhythmia, atrial fibrillation, venous thrombosis and associated phlebitis.

The timetable you submitted on December 17, 2008 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	August 2009
Study Completion Date:	February 2010
Final Report Submission:	February 2017

Submit the protocol to your IND 9869, with a cross-reference letter to this BLA 125160. Submit all final report(s) to your BLA 125160. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study requirement as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING STUDY COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS OF 21 CFR 601.70

2. To re-evaluate the drug product sub-visible release and shelf-life specifications upon confirming the feasibility of a preparatory method that will enable implementation of the USP <788> preferred method. Data and specification assessment will be provided within 2 years from the time of approval.

   Study Completion: January 2011
   Final Report Submission: April 2011

3. Provide a commitment to conduct additional studies to evaluate the process-specific assay test for the assessment of HCP per your July 31, 2008 submission. A summary report and data will be provided by June 30, 2009.

   Study Completion: June 2009
   Final Report Submission: July 2009

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that CIMZIA® poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of CIMZIA®. FDA has determined that CIMZIA™ is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use CIMZIA®. In addition, patient labeling could help prevent serious adverse effects related to the use of the product. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed CIMZIA®.

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS is approved. The REMS consists of the Medication Guide, the communication plan included with this letter, and the timetable for submission of assessments of the REMS included in your March 12, 2009 submission.

Information needed for assessment of the REMS should include but not be limited to:

a. Survey of patients' understanding of the serious risks of CIMZIA®

b. Report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
d. Survey of physicians' understanding of the serious risks of CIMZIA®

Use the following designator to prominently label all submissions, including supplements, relating to this REMS:

Risk Evaluation and Mitigation Strategy (REMS)

PROMOTIONAL MATERIALS

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this BLA and to the following address:

MedWatch, HFD-001
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the following address:

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the following address:

Division of Compliance Risk Management and Surveillance
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20903

Biological product deviations sent by courier or overnight mail should also be sent to this address.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging, or labeling of certolizumab pegol or in the manufacturing facilities.

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original BLA 125160 for this drug product. In the future, do not make submissions to this BLA except for the final printed labeling requested above.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Kathleen Davies, Regulatory Project Manager, at (301) 796-2205.

Sincerely,

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures (3):
Package Insert
Patient Package Insert
Carton and Immediate Container Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125271/0

COMPLETE RESPONSE

JAN 2 2009

UCB, Inc.
1950 Lake Park Drive
Smyrna, GA 30080

Attention: Sandra Bonsall, RAC
Associate Director, Regulatory Affairs

Dear Ms. Bonsall:

Please refer to your biologics license application, dated November 29, 2007, received December 6, 2007, submitted under section 351 of the Public Health Service Act for CIMZIA® (certolizumab pegol) for the treatment of rheumatoid arthritis.

We acknowledge receipt of your submissions dated February 15, March 14, April 3, May 16 and 30, July 18, August 11, 12, 14 and 20, 25 and 28, September 3, 9, 10, 15, and 30, October 14 and 21, November 21, December 12, 18, 19, 22 and 24, 2008.

The September 30, 2008, amendment constituted a major amendment.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

In the clinical studies submitted with this application there appears to be an increased risk of cardiovascular adverse events in the CIMZIA® treatment arms compared to the placebo treatment arms. Provide further data to clarify the cardiovascular risks of the proposed doses and/or provide data on the safety and efficacy of lower doses of CIMZIA® in order to assure us that a dose level(s) with favorable risk-benefit characteristics has been defined. This may be accomplished by reanalysis of the available data or it may require an additional adequate and well-controlled study focused primarily on cardiovascular adverse events.

RISK EVALUATION MITIGATION STRATEGY REQUIREMENTS

A revised risk evaluation and mitigation strategy (REMS) for CIMZIA® was approved on December 31, 2008, under BLA 125160/38. That approved REMS consisted of a Medication Guide revised to address the risks of serious infections, including opportunistic infections, that have been associated with treatment with TNFα blockers such as CIMZIA®, a communication plan, and a timetable for assessment. We have determined that a REMS is necessary to ensure that the benefits of CIMZIA outweigh its risks for patients with rheumatoid arthritis because the risks addressed in the REMS are risks that could be expected to affect any patient population taking CIMZIA®. You should submit the revised REMS to BLA 125271 with modifications to the Medication Guide to reflect the rheumatoid arthritis indication and with modifications to ensure that the communication plan reaches physicians, such as rheumatologists, who may prescribe CIMZIA® for rheumatoid arthritis. The timetable for submission of assessments of the REMS should remain the same as in the REMS approved on April 22, 2008, with the original approval of CIMZIA®.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the initial submission.
   - Present tabulations of the new safety data combined with the initial data.
   - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the initial data.

6. Provide updated exposure information for the clinical trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

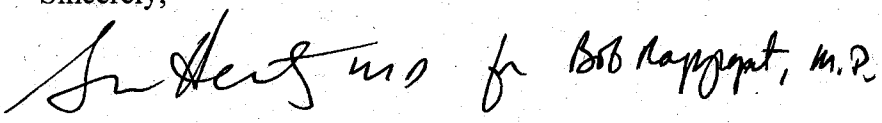
Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application can be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call the Regulatory Project Manager, Kathleen Davies, at (301) 796-2205.

Sincerely,



Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

LABELING

Cimzia®
(certolizumab pegol)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CIMZIA® safely and effectively. See full prescribing information for CIMZIA.

CIMZIA (certolizumab pegol)
Lyophilized powder for solution and solution for subcutaneous injection
Initial U.S. Approval: 2008

WARNING: RISK OF SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.

- **Increased risk of serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.**
- **CIMZIA should be discontinued if a patient develops a serious infection or sepsis.**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting CIMZIA.**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Rheumatoid Arthritis (1.2)	05/2009
Dosage and Administration, Rheumatoid Arthritis (2)	05/2009
Warnings and Precautions, Use with Biological DMARDs (5.8)	05/2009
Boxed Warning, Risk of Serious Infections	12/2008
Warnings and Precautions, Risk of Serious Infections (5.1)	12/2008

----------INDICATIONS AND USAGE----------
CIMZIA is a tumor necrosis factor (TNF) blocker indicated for:

- Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy (1.1)
- Treatment of adults with moderately to severely active rheumatoid arthritis (1.2)

----------DOSAGE AND ADMINISTRATION----------
CIMZIA is administered by subcutaneous injection. The initial dose of CIMZIA is 400 mg (given as two subcutaneous injections of 200 mg).

Crohn's Disease (2.1)

- 400 mg initially and at Weeks 2 and 4. If response occurs, follow with 400 mg every four weeks

Rheumatoid Arthritis (2.2)

- 400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered

----------DOSAGE FORMS AND STRENGTHS----------

- 200 mg lyophilized powder for reconstitution with 1 mL of sterile Water for Injection, USP (3)
- 200 mg/mL in a single-use prefilled glass syringe (3)

----------CONTRAINDICATIONS----------

- None (4)

----------WARNINGS AND PRECAUTIONS----------

- Serious infections – do not start CIMZIA during an active infection. If an infection develops, monitor carefully, and stop CIMZIA if infection becomes serious (5.1)
- Cases of lymphoma and other malignancies have been observed among patients receiving TNF blockers (5.2)
- Heart failure, worsening or new onset may occur (5.3)
- Anaphylaxis or serious allergic reactions may occur (5.4)
- Hepatitis B virus reactivation – monitor HBV carriers during and several months after therapy. If reactivation occurs, stop CIMZIA and begin anti-viral therapy (5.5)
- Demyelinating disease, exacerbation or new onset, may occur (5.6)
- Cytopenias, pancytopenia – advise patients to seek immediate medical attention if symptoms develop, and consider stopping CIMZIA (5.7)
- Lupus-like syndrome – stop CIMZIA if syndrome develops (5.9)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥7% and higher than placebo): upper respiratory tract infection, rash, and urinary tract infection (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at 1-866-822-0068 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Use with Biological DMARDs – increased risk of serious infections (5.8, 7.1)
- Live vaccines – do not give with CIMZIA (5.10, 7.2)
- Laboratory tests – may interfere with aPTT tests (7.3)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: 05/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

Cimzia®
(certolizumab pegol)

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with CIMZIA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

CIMZIA should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before CIMZIA use and during therapy. Treatment for latent infection should be initiated prior to CIMZIA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with CIMZIA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Crohn's Disease

CIMZIA is indicated for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

1.2 Rheumatoid Arthritis

CIMZIA is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis (RA).

2 DOSAGE AND ADMINISTRATION

CIMZIA is administered by subcutaneous injection. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red or hard. When a 400 mg dose is needed (given as two subcutaneous injections of 200 mg), injections should occur at separate sites in the thigh or abdomen.

The solution should be carefully inspected visually for particulate matter and discoloration prior to administration. The solution should be a clear colorless to yellow liquid, essentially free from particulates and should not be used if cloudy or if foreign particulate matter is present. CIMZIA does

not contain preservatives; therefore, unused portions of drug remaining in the syringe or vial should be discarded.

2.1 Crohn's Disease

The recommended initial adult dose of CIMZIA is 400 mg (given as two subcutaneous injections of 200 mg) initially, and at Weeks 2 and 4. In patients who obtain a clinical response, the recommended maintenance regimen is 400 mg every four weeks.

2.2 Rheumatoid Arthritis

The recommended dose of CIMZIA for adult patients with rheumatoid arthritis is 400 mg (given as two subcutaneous injections of 200 mg) initially and at Weeks 2 and 4, followed by 200 mg every other week. For maintenance dosing, CIMZIA 400 mg every 4 weeks can be considered *[see Clinical Studies (14.2)]*.

2.3 Preparation and Administration of CIMZIA Using the Lyophilized Powder for Solution

The lyophilized powder should be prepared and administered by a health care professional. CIMZIA is provided in a package that contains everything required to reconstitute and inject the drug as described below. CIMZIA should be brought to room temperature before reconstituting to facilitate dissolution.

Reconstitute each lyophilized vial of CIMZIA using appropriate aseptic technique, with 1 mL of sterile Water for Injection, USP, and a syringe with a 20 gauge needle. Gently swirl each vial of CIMZIA without shaking so that all of the lyophilized powder comes into contact with the sterile Water for Injection. Leave the vials undisturbed to fully reconstitute (this may take as long as 30 minutes). Reconstituted CIMZIA has a concentration of approximately 200 mg/mL. Once reconstituted, CIMZIA is a clear to opalescent, colorless to pale yellow liquid essentially free from particulates.

Prior to injecting, reconstituted CIMZIA should be at room temperature. Do not leave reconstituted CIMZIA at room temperature for more than 2 hours prior to administration. Using a new 20 gauge (reconstitution) needle for each vial, withdraw the reconstituted solution into a separate syringe for each vial, so that each syringe contains 1 mL of CIMZIA (200 mg of certolizumab pegol). Switch each 20 gauge needle to a 23 gauge (dosing) needle and inject the full contents of each syringe subcutaneously into the thigh or abdomen. Where a 400 mg dose is required, separate sites should be used for each 200 mg injection.

Once reconstituted, CIMZIA can be stored in the vials for up to 24 hours at 2 to 8°C (36 to 46 °F) prior to injection. Do not freeze.

2.4 Preparation and Administration of CIMZIA Using the Prefilled Syringe

A patient may self-inject CIMZIA if a physician determines that it is appropriate, with medical follow-up, as necessary, after proper training in subcutaneous injection technique.

Patients using CIMZIA should be instructed to inject the full amount in the syringe (1 mL), according to the directions provided in the Patient Instructions for Use [*see FDA approved Medication Guide (17.3)*].

2.5 Monitoring to Assess Safety

Before initiation of therapy with CIMZIA, all patients must be evaluated for both active and inactive (latent) tuberculosis infection. The possibility of undetected latent tuberculosis should be considered in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. Appropriate screening tests (e.g. tuberculin skin test and chest x-ray) should be performed in all patients.

2.6 Concomitant Medications

CIMZIA may be used as monotherapy or concomitantly with non-biological disease modifying anti-rheumatic drugs (DMARDs). In rheumatoid arthritis clinical studies, patients on CIMZIA therapy also took concomitant methotrexate (MTX) with the recommended CIMZIA dose of 200 mg every other week. CIMZIA should not be used in combination with biological DMARDs or other tumor necrosis factor (TNF) blocker therapy.

3 DOSAGE FORMS AND STRENGTHS

- **Lyophilized Powder for Reconstitution**
  Sterile, white, lyophilized powder for reconstitution and then subcutaneous administration. Each single-use vial provides approximately 200 mg of CIMZIA.
- **Prefilled Syringe**
  A single-use, 1 mL prefilled glass syringe with a fixed 25 gauge ½ inch thin wall needle, providing 200 mg (1 mL) of CIMZIA.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Infections (see also Boxed Warning)

Serious and sometimes fatal infection due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens has been reported in patients receiving TNF-blocking agents. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most common. Patients have frequently presented with disseminated rather than localized disease, and are often taking concomitant immunosuppressants such as methotrexate or corticosteroids with CIMZIA.

Treatment with CIMZIA should not be initiated in patients with an active infection, including clinically important localized infections. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis
- with underlying conditions that may predispose them to infection

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving CIMZIA, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating CIMZIA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF-blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating CIMZIA, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Anti-tuberculosis therapy should also be considered prior to initiation of CIMZIA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision of whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Tuberculosis should be strongly considered in patients who develop a new infection during CIMZIA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with CIMZIA.

CIMZIA should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with CIMZIA should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and risks of antifungal therapy.

5.2 Malignancies

In the controlled portions of clinical studies of some TNF blockers, more cases of malignancies have been observed among patients receiving TNF blockers compared to control patients. During controlled and open-labeled portions of CIMZIA studies of Crohn's disease and other diseases, malignancies (excluding non-melanoma skin cancer) were observed at a rate (95% confidence interval) of 0.5 (0.4, 0.7) per 100 patient-years among 4,650 CIMZIA-treated patients versus a rate of 0.6 (0.1, 1.7) per 100 patient-years among 1,319 placebo-treated patients. The size of the control group and limited duration of the controlled portions of the studies precludes the ability to draw firm conclusions.

In the controlled portions of clinical trials of all the TNF blockers, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. In controlled studies of CIMZIA for Crohn's disease and other investigational uses, there was one case of lymphoma among 2,657 Cimzia-treated patients and one case of Hodgkin's lymphoma among 1,319 placebo-treated patients.

In the CIMZIA RA clinical trials (placebo-controlled and open label) a total of three cases of lymphoma were observed among 2,367 patients. This is approximately 2-fold higher than expected in the general population. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma.

Rates in clinical studies for CIMZIA cannot be compared to the rates of clinical trials of other TNF blockers and may not predict the rates observed when CIMZIA is used in a broader patient population. Patients with Crohn's disease that require chronic exposure to immunosuppressant therapies may be at higher risk than the general population for the development of lymphoma, even in

the absence of TNF blocker therapy. The potential role of TNF blocker therapy in the development of malignancies is not known *[see Adverse Reactions (6.1)]*.

5.3 Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including CIMZIA. CIMZIA has not been formally studied in patients with CHF; however, in clinical studies in patients with CHF with another TNF blocker, worsening congestive heart failure (CHF) and increased mortality due to CHF were observed. Exercise caution in patients with heart failure and monitor them carefully [see *Adverse Reactions (6.1)]*.

5.4 Hypersensitivity Reactions

The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, dyspnea, hypotension, rash, serum sickness, and urticaria. If such reactions occur, discontinue further administration of CIMZIA and institute appropriate therapy. There are no data on the risks of using CIMZIA in patients who have experienced a severe hypersensitivity reaction towards another TNF blocker; in these patients caution is needed *[see Adverse Reactions (6.1)]*.

5.5 Hepatitis B Virus Reactivation

Use of TNF blockers, including CIMZIA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation.

Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating CIMZIA therapy. Exercise caution in prescribing CIMZIA for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with CIMZIA should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy.

In patients who develop HBV reactivation, discontinue CIMZIA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of CIMZIA therapy in this situation and monitor patients closely.

5.6 Neurologic Reactions

Use of TNF blockers, including CIMZIA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Exercise caution in considering the use of CIMZIA in patients with pre-existing or recent-onset central nervous system demyelinating disorders. Rare cases of neurological disorders, including seizure disorder, optic neuritis, and peripheral neuropathy have been reported in patients treated with CIMZIA; the causal relationship to CIMZIA remains unclear *[see Adverse Reactions (6.1)]*.

5.7 Hematological Reactions

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., leukopenia, pancytopenia, thrombocytopenia) have been infrequently reported with CIMZIA *[see Adverse Reactions (6.1)]*. The causal relationship of these events to CIMZIA remains unclear.

Although no high risk group has been identified, exercise caution in patients being treated with CIMZIA who have ongoing, or a history of, significant hematologic abnormalities. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood

dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on CIMZIA. Consider discontinuation of CIMZIA therapy in patients with confirmed significant hematologic abnormalities.

5.8 Use with Biological Disease-Modifying Antirheumatic Drugs (Biological DMARDs)

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF blocker, etanercept, with no added benefit compared to entanercept alone. A higher risk of serious infections was also observed in combination use of TNF blockers with abatacept and rituximab. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the use of CIMZIA in this combination. Therefore, the use of CIMZIA in combination with other biological DMARDs is not recommended *[see Drug Interactions (7.1)]*.

5.9 Autoimmunity

Treatment with CIMZIA may result in the formation of autoantibodies and rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with CIMZIA, discontinue treatment *[see Adverse Reactions (6.1)]*.

5.10 Immunizations

No data are available on the response to vaccinations or the secondary transmission of infection by live vaccines in patients receiving CIMZIA. Do not administer live vaccines or attenuated vaccines concurrently with CIMZIA.

5.11 Immunosuppression

Since TNF mediates inflammation and modulates cellular immune responses, the possibility exists for TNF blockers, including CIMZIA, to affect host defenses against infections and malignancies. The impact of treatment with CIMZIA on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood *[see Warnings and Precautions (5.1, 5.2, 5.5) and Adverse Reactions (6.1)]*. The safety and efficacy of CIMZIA in patients with immunosuppression has not been formally evaluated.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The most serious adverse reactions were:

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.2)]*
- Heart Failure *[see Warnings and Precautions (5.3)]*

In premarketing controlled trials of all patient populations combined the most common adverse reactions (≥ 8%) were upper respiratory infections (18%), rash (9%) and urinary tract infections (8%).

Adverse Reactions Most Commonly Leading to Discontinuation of Treatment in Premarketing Controlled Trials

The proportion of patients with Crohn's disease who discontinued treatment due to adverse reactions in the controlled clinical studies was 8% for CIMZIA and 7% for placebo. The most common adverse reactions leading to the discontinuation of CIMZIA (for at least 2 patients and with a higher incidence than placebo) were abdominal pain (0.4% CIMZIA, 0.2% placebo), diarrhea (0.4% CIMZIA, 0% placebo), and intestinal obstruction (0.4% CIMZIA, 0% placebo).

The proportion of patients with rheumatoid arthritis who discontinued treatment due to adverse reactions in the controlled clinical studies was 5% for CIMZIA and 2.5% for placebo. The

most common adverse reactions leading to discontinuation of CIMZIA were tuberculosis infections (0.5%); and pyrexia, urticaria, pneumonia, and rash (0.3%).

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

Controlled Studies with Crohn's Disease

The data described below reflect exposure to CIMZIA at 400 mg subcutaneous dosing in studies of patients with Crohn's disease. In the safety population in controlled studies, a total of 620 patients with Crohn's disease received CIMZIA at a dose of 400 mg, and 614 subjects received placebo (including subjects randomized to placebo in Study CD2 following open label dosing of CIMZIA at Weeks 0, 2, 4). In controlled and uncontrolled studies, 1,564 patients received CIMZIA at some dose level, of whom 1,350 patients received 400 mg CIMZIA. Approximately 55% of subjects were female, 45% were male, and 94% were Caucasian. The majority of patients in the active group were between the ages of 18 and 64.

During controlled clinical studies, the proportion of patients with serious adverse reactions was 10% for CIMZIA and 9% for placebo. The most common adverse reactions (occurring in ≥ 5% of CIMZIA-treated patients, and with a higher incidence compared to placebo) in controlled clinical studies with CIMZIA were upper respiratory infections (e.g. nasopharyngitis, laryngitis, viral infection) in 20% of CIMZIA-treated patients and 13% of placebo-treated patients, urinary tract infections (e.g. bladder infection, bacteriuria, cystitis) in 7% of CIMZIA-treated patients and in 6% of placebo-treated patients, and arthralgia (6% CIMZIA, 4% placebo).

Other Adverse Reactions

The most commonly occurring adverse reactions in controlled trials of Crohn's disease were described above. Other serious or significant adverse reactions reported in controlled and uncontrolled studies in Crohn's disease and other diseases, occurring in patients receiving CIMZIA at doses of 400 mg or other doses include:

Blood and lymphatic system disorders: Anemia, leukopenia, lymphadenopathy, pancytopenia, and thrombophilia.

Cardiac disorders: Angina pectoris, arrhythmias, atrial fibrillation, cardiac failure, hypertensive heart disease, myocardial infarction, myocardial ischemia, pericardial effusion, pericarditis, stroke and transient ischemic attack.

Eye disorders: Optic neuritis, retinal hemorrhage, and uveitis.

General disorders and administration site conditions: Bleeding and injection site reactions.

Hepatobiliary disorders: Elevated liver enzymes and hepatitis.

Immune system disorders: Alopecia totalis.

Psychiatric disorders: Anxiety, bipolar disorder, and suicide attempt.

Renal and urinary disorders: Nephrotic syndrome and renal failure.

Reproductive system and breast disorders: Menstrual disorder.

Skin and subcutaneous tissue disorders: Dermatitis, erythema nodosum, and urticaria.

Vascular disorders: Thrombophlebitis, vasculitis.

Controlled Studies with Rheumatoid Arthritis

CIMZIA was studied primarily in placebo-controlled trials and in long-term follow-up studies. The data described below reflect the exposure to CIMZIA in 2,367 RA patients, including 2,030 exposed for at least 6 months, 1,663 exposed for at least one year and 282 for at least 2 years; and 1,774 in adequate and well-controlled studies. In placebo-controlled studies, the population had a median age of 53 years at entry; approximately 80% were females, 93% were Caucasian and all patients were suffering from active rheumatoid arthritis, with a median disease duration of 6.2 years. Most patients received the recommended dose of CIMZIA or higher.

Table 1 summarizes the reactions reported at a rate of at least 3% in patients treated with CIMZIA 200 mg every other week compared to placebo (saline formulation), given concomitantly with methotrexate.

Table 1: Adverse Reactions Reported by ≥3% of Patients Treated with CIMZIA Dosed Every Other Week during Placebo-Controlled Period of Rheumatoid Arthritis Studies, with Concomitant Methotrexate.

Adverse Reaction (Preferred Term)	Placebo+ MTX[#] (%) N =324	CIMZIA 200 mg EOW + MTX(%) N =640
Upper respiratory tract infection	2	6
Headache	4	5
Hypertension	2	5
Nasopharyngitis	1	5
Back pain	1	4
Pyrexia	2	3
Pharyngitis	1	3
Rash	1	3
Acute bronchitis	1	3
Fatigue	2	3

[#]EOW = Every other Week, MTX = Methotrexate.

Hypertensive adverse reactions were observed more frequently in patients receiving CIMZIA than in controls. These adverse reactions occurred more frequently among patients with a baseline history of hypertension and among patients receiving concomitant corticosteroids and non-steroidal anti-inflammatory drugs.

Patients receiving CIMZIA 400 mg as monotherapy every 4 weeks in rheumatoid arthritis controlled clinical trials had similar adverse reactions to those patients receiving CIMZIA 200 mg every other week.

Other Adverse Reactions

Other infrequent adverse reactions (occurring in less than 3% of RA patients) were similar to those seen in Crohn's disease patients.

Infections

The incidence of infections in controlled studies in Crohn's disease was 38% for CIMZIA-treated patients and 30% for placebo-treated patients. The infections consisted primarily of upper respiratory infections (20% for CIMZIA, 13% for placebo). The incidence of serious infections during the controlled clinical studies was 3% per patient-year for CIMZIA-treated patients and 1% for placebo-treated patients. Serious infections observed included bacterial and viral infections, pneumonia, and pyelonephritis.

The incidence of new cases of infections in controlled clinical studies in rheumatoid arthritis was 0.91 per patient-year for all CIMZIA-treated patients and 0.72 per patient-year for placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, herpes infections, urinary tract infections, and lower respiratory tract infections. In the controlled rheumatoid arthritis studies, there were more new cases of serious infection adverse reactions in the CIMZIA treatment groups, compared to the placebo groups (0.06 per patient-year for all CIMZIA doses vs. 0.02 per patient-year for placebo). Rates of serious infections in the 200 mg every other week dose group were 0.06 per patient-year and in the 400 mg every 4 weeks dose group were 0.04 per patient-year. Serious infections included tuberculosis, pneumonia, cellulitis, and pyelonephritis. In the placebo group, no serious infection occurred in more than one subject. There is no evidence of increased risk of infections with continued exposure over time *[see Warnings and Precautions (5.1)]*.

Tuberculosis and Opportunistic Infections

In completed and ongoing global clinical studies in all indications including 5,118 CIMZIA-treated patients, the overall rate of tuberculosis is approximately 0.61 per 100 patient-years across all indications.

The majority of cases occurred in countries with high endemic rates of TB. No cases of TB (0/980) have been reported in the US or Canada across all indications. Reports include cases of miliary, lymphatic, peritoneal, as well as pulmonary TB. The median time to onset of TB for all patients exposed to CIMZIA across all indications was 345 days. In the studies with CIMZIA in RA, there were 36 cases of TB among 2,367 exposed patients, including some fatal cases. Rare cases of opportunistic infections have also been reported in these clinical trials. *[see Warnings and Precautions (5.1)]*.

Malignancies

In clinical studies of CIMZIA, the overall incidence rate of malignancies was similar for CIMZIA-treated and control patients. For some TNF blockers, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients. *[see Warnings and Precautions (5.2)]*

Heart Failure

In placebo-controlled and open-label rheumatoid arthritis studies, cases of new or worsening heart failure have been reported for CIMZIA-treated patients. The majority of these cases were mild to moderate and occurred during the first year of exposure. *[see Warnings and Precautions (5.3)]*.

Autoantibodies

In clinical studies in Crohn's disease, 4% of patients treated with CIMZIA and 2% of patients treated with placebo that had negative baseline ANA titers developed positive titers during the studies. One of the 1,564 Crohn's disease patients treated with CIMZIA developed symptoms of a lupus-like syndrome.

In clinical trials of TNF blockers, including CIMZIA, in patients with RA, some patients have developed ANA. Four patients out of 2,367 patients treated with CIMZIA in RA clinical studies developed clinical signs suggestive of a lupus-like syndrome. The impact of long-term treatment with

CIMZIA on the development of autoimmune diseases is unknown *[see Warnings and Precautions (5.9)]*.

Immunogenicity

Patients were tested at multiple time points for antibodies to certolizumab pegol during Studies CD1 and CD2. The overall percentage of antibody positive patients was 8% in patients continuously exposed to CIMZIA, approximately 6% were neutralizing *in vitro*. No apparent correlation of antibody development to adverse events or efficacy was observed. Patients treated with concomitant immunosuppressants had a lower rate of antibody development than patients not taking immunosuppressants at baseline (3% and 11%, respectively). The following adverse events were reported in Crohn's disease patients who were antibody-positive (N = 100) at an incidence at least 3% higher compared to antibody-negative patients (N = 1,242): abdominal pain, arthralgia, edema peripheral, erythema nodosum, injection site erythema, injection site pain, pain in extremity, and upper respiratory tract infection.

The overall percentage of patients with antibodies to certolizumab pegol detectable on at least one occasion was 7% (105 of 1,509) in the rheumatoid arthritis placebo-controlled trials. Approximately one third (3%, 39 of 1,509) of these patients had antibodies with neutralizing activity *in vitro*. Patients treated with concomitant immunosuppressants (MTX) had a lower rate of antibody development than patients not taking immunosuppressants at baseline. Patients treated with concomitant immunosuppressant therapy (MTX) in RA-I, RA-II, RA-III had a lower rate of neutralizing antibody formation overall than patients treated with CIMZIA monotherapy in RA-IV (2% vs. 8%). Both the loading dose of 400 mg every other week at Weeks 0, 2 and 4 and concomitant use of MTX were associated with reduced immunogenicity.

Antibody formation was associated with lowered drug plasma concentration and reduced efficacy. In patients receiving the recommended CIMZIA dosage of 200 mg every other week with concomitant MTX, the ACR20 response was lower among antibody positive patients than among antibody-negative patients (Study RA-I, 48% versus 60%; Study RA-II 35% versus 59%, respectively). In Study RA-III, too few patients developed antibodies to allow for meaningful analysis of ACR20 response by antibody status. In Study RA-IV (monotherapy), the ACR20 response was 33% versus 56%, antibody-positive versus antibody-negative status, respectively. *[see Clinical Pharmacology (12.3)]*. No association was seen between antibody development and the development of adverse events.

The data reflect the percentage of patients whose test results were considered positive for antibodies to certolizumab pegol in an ELISA, and are highly dependent on the sensitivity and specificity of the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to certolizumab pegol with the incidence of antibodies to other products may be misleading.

Hypersensitivity Reactions

The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, dermatitis allergic, dizziness (postural), dyspnea, hot flush, hypotension, injection site reactions, malaise, pyrexia, rash, serum sickness, and (vasovagal) syncope *[see Warnings and Precautions (5.4)]*.

6.2 Adverse Reaction Information from Other Sources

Cases of severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme, have been identified during post-approval use of other TNF blockers. Because these reactions are reported voluntarily from a population of uncertain size, it is

not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

7.1 Use with Anakinra, Abatacept, Rituximab, and Natalizumab

An increased risk of serious infections has been seen in clinical studies of other TNF-blocking agents used in combination with anakinra or abatacept, with no added benefit. Formal drug interaction studies have not been performed with rituximab or natalizumab. Because of the nature of the adverse events seen with these combinations with TNF blocker therapy, similar toxicities may also result from the use of CIMZIA in these combinations. There is not enough information to assess the safety and efficacy of such combination therapy. Therefore, the use of CIMZIA in combination with anakinra, abatacept, rituximab, or natalizumab is not recommended *[see Warnings and Precautions (5.8)]*.

7.2 Live Vaccines

Do not give live (including attenuated) vaccines concurrently with CIMZIA *[see Warnings and Precautions (5.10)]*.

7.3 Laboratory Tests

Interference with certain coagulation assays has been detected in patients treated with CIMZIA. Certolizumab pegol may cause erroneously elevated activated partial thromboplastin time (aPTT) assay results in patients without coagulation abnormalities. This effect has been observed with the PTT-Lupus Anticoagulant (LA) test and Standard Target Activated Partial Thromboplastin time (STA-PTT) Automate tests from Diagnostica Stago, and the HemosIL APTT-SP liquid and HemosIL lyophilized silica tests from Instrumentation Laboratories. Other aPTT assays may be affected as well. Interference with thrombin time (TT) and prothrombin time (PT) assays has not been observed. There is no evidence that CIMZIA therapy has an effect on *in vivo* coagulation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B – Because certolizumab pegol does not cross-react with mouse or rat TNFα, reproduction studies were performed in rats using a rodent anti-murine TNFα pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol. Reproduction studies have been performed in rats at doses up to 100 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to cTN3 PF. There are, however, no adequate and well-controlled studies of CIMZIA in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CIMZIA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of CIMZIA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience

has not identified differences in responses between the elderly and younger patients. Population pharmacokinetic analyses of patients enrolled in CIMZIA clinical studies concluded that there was no apparent difference in drug concentration regardless of age. Because there is a higher incidence of infections in the elderly population in general, use caution when treating the elderly with CIMZIA *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

The maximum tolerated dose of certolizumab pegol has not been established. Doses of up to 800 mg subcutaneous and 20 mg/kg intravenous have been administered without evidence of dose-limiting toxicities. In cases of overdosage, it is recommended that patients be monitored closely for any adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

CIMZIA (certolizumab pegol) is a TNF blocker. CIMZIA is a recombinant, humanized antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNFα), conjugated to an approximately 40kDa polyethylene glycol (PEG2MAL40K). The Fab' fragment is manufactured in *E. coli* and is subsequently subjected to purification and conjugation to PEG2MAL40K, to generate certolizumab pegol. The Fab' fragment is composed of a light chain with 214 amino acids and a heavy chain with 229 amino acids. The molecular weight of certolizumab pegol is approximately 91 kiloDaltons.

CIMZIA is supplied as either a sterile, white, lyophilized powder for solution or as a sterile, solution in a single-use prefilled 1 mL glass syringe for subcutaneous injection. After reconstitution of the lyophilized powder with 1 mL sterile Water for Injection, USP, the resulting pH is approximately 5.2. Each single-use vial provides approximately 200 mg certolizumab pegol, 100 mg sucrose, 0.9 mg lactic acid, and 0.1 mg polysorbate.

Each prefilled syringe delivers 1 mL (200 mg) of drug product with a pH of approximately 4.7. Each 1 mL syringe of CIMZIA contains 200 mg of certolizumab pegol, 1.36 mg of sodium acetate, 7.31 mg sodium chloride, and Water for Injection, USP.

CIMZIA is a clear to opalescent solution that is colorless to pale yellow and essentially free from particulates. No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Certolizumab pegol binds to human TNFα with a KD of 90pM. TNFα is a key pro-inflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralizes TNFα (IC_{90} of 4 ng/mL for inhibition of human TNFα in the *in vitro* L929 murine fibrosarcoma cytotoxicity assay) but does not neutralize lymphotoxin α (TNFβ). Certolizumab pegol cross-reacts poorly with TNF from rodents and rabbits, therefore *in vivo* efficacy was evaluated using animal models in which human TNFα was the physiologically active molecule.

Certolizumab pegol was shown to neutralize membrane-associated and soluble human TNFα in a dose-dependent manner. Incubation of monocytes with certolizumab pegol resulted in a dose-dependent inhibition of LPS-induced TNFα and IL-1β production in human monocytes.

Certolizumab pegol does not contain a fragment crystallizable (Fc) region, which is normally present in a complete antibody, and therefore does not fix complement or cause antibody-dependent cell-mediated cytotoxicity *in vitro*. It does not induce apoptosis *in vitro* in human peripheral blood-derived monocytes or lymphocytes, nor does certolizumab pegol induce neutrophil degranulation.

A tissue reactivity study was carried out *ex vivo* to evaluate potential cross-reactivity of certolizumab pegol with cryosections of normal human tissues. Certolizumab pegol showed no reactivity with a designated standard panel of normal human tissues.

12.2 Pharmacodynamics

Biological activities ascribed to TNFα include the upregulation of cellular adhesion molecules and chemokines, upregulation of major histocompatibility complex (MHC) class I and class II molecules, and direct leukocyte activation. TNFα stimulates the production of downstream inflammatory mediators, including interleukin-1, prostaglandins, platelet activating factor, and nitric oxide. Elevated levels of TNFα have been implicated in the pathology of Crohn's disease and rheumatoid arthritis. Certolizumab pegol binds to TNFα, inhibiting its role as a key mediator of inflammation. TNFα is strongly expressed in the bowel wall in areas involved by Crohn's disease and fecal concentrations of TNFα in patients with Crohn's disease have been shown to reflect clinical severity of the disease. After treatment with certolizumab pegol, patients with Crohn's disease demonstrated a decrease in the levels of C-reactive protein (CRP). Increased TNFα levels are found in the synovial fluid of rheumatoid arthritis patients and play an important role in the joint destruction that is a hallmark of this disease.

12.3 Pharmacokinetics

- **Absorption**

A total of 126 healthy subjects received doses of up to 800 mg certolizumab pegol subcutaneously (sc) and up to 10 mg/kg intravenously (IV) in four pharmacokinetic studies. Data from these studies demonstrate that single intravenous and subcutaneous doses of certolizumab pegol have predictable dose-related plasma concentrations with a linear relationship between the dose administered and the maximum plasma concentration (C_{max}), and the Area Under the certolizumab pegol plasma concentration versus time Curve (AUC). A mean C_{max} of approximately 43 to 49 mcg/mL occurred at Week 5 during the initial loading dose period using the recommended dose regimen for the treatment of patients with rheumatoid arthritis (400 mg sc at Weeks 0, 2 and 4 followed by 200 mg every other week).

Certolizumab pegol plasma concentrations were broadly dose-proportional and pharmacokinetics observed in patients with rheumatoid arthritis and Crohn's disease were consistent with those seen in healthy subjects.

Following subcutaneous administration, peak plasma concentrations of certolizumab pegol were attained between 54 and 171 hours post-injection. Certolizumab pegol has bioavailability (F) of approximately 80% (ranging from 76% to 88%) following subcutaneous administration compared to intravenous administration.

- **Distribution**

The steady state volume of distribution (Vss) was estimated as 6 to 8 L in the population pharmacokinetic analysis for patients with Crohn's disease and patients with rheumatoid arthritis.

- **Metabolism**

The metabolism of certolizumab pegol has not been studied in human subjects. Data from animals indicate that once cleaved from the Fab' fragment the PEG moiety is mainly excreted in urine without further metabolism.

- **Elimination**

PEGylation, the covalent attachment of PEG polymers to peptides, delays the metabolism and elimination of these entities from the circulation by a variety of mechanisms, including decreased renal clearance, proteolysis, and immunogenicity. Accordingly, certolizumab pegol is an antibody Fab' fragment conjugated with PEG in order to extend the terminal plasma elimination half-life ($t_{1/2}$) of the Fab'. The terminal elimination phase half-life ($t_{1/2}$) was approximately 14 days for all doses tested. The clearance following IV administration to healthy subjects ranged from 9.21 mL/h to 14.38 mL/h. The clearance following sc dosing was estimated 17 mL/h in the Crohn's disease population PK analysis with an inter-subject variability of 38% (CV) and an inter-occasion variability of 16%.

Similarly, the clearance following sc dosing was estimated as 21.0 mL/h in the RA population PK analysis, with an inter-subject variability of 30.8% (%CV) and inter-occasion variability 22.0%. The route of elimination of certolizumab pegol has not been studied in human subjects. Studies in animals indicate that the major route of elimination of the PEG component is via urinary excretion.

- **Special Populations**

Population pharmacokinetic analysis was conducted on data from patients with rheumatoid arthritis and patients with Crohn's disease, to evaluate the effect of age, race, gender, methotrexate use, concomitant medication, creatinine clearance and presence of anti-certolizumab antibodies on pharmacokinetics of certolizumab pegol.

Only bodyweight and presence of anti-certolizumab antibodies significantly affected certolizumab pegol pharmacokinetics. Pharmacokinetic exposure was inversely related to body weight but pharmacodynamic exposure-response analysis showed that no additional therapeutic benefit would be expected from a weight-adjusted dose regimen. The presence of anti-certolizumab antibodies was associated with a 3.6-fold increase in clearance.

Age: Pharmacokinetics of certolizumab pegol was not different in elderly compared to young adults.

Gender: Pharmacokinetics of certolizumab pegol was similar in male and female subjects.

Renal Impairment: Specific clinical studies have not been performed to assess the effect of renal impairment on the pharmacokinetics of CIMZIA. The pharmacokinetics of the PEG (polyethylene glycol) fraction of certolizumab pegol is expected to be dependent on renal function but has not been assessed in renal impairment. There are insufficient data to provide a dosing recommendation in moderate and severe renal impairment.

Race: A specific clinical study showed no difference in pharmacokinetics between Caucasian and Japanese subjects.

- **Drug Interaction Studies**

Methotrexate pharmacokinetics is not altered by concomitant administration with CIMZIA in patients with rheumatoid arthritis. The effect of methotrexate on CIMZIA pharmacokinetics was not studied. However, methotrexate-treated patients have lower incidence of antibodies to CIMZIA. Thus, therapeutic plasma levels are more likely to be sustained when CIMZIA is administered with methotrexate in patients with rheumatoid arthritis.

Formal drug-drug interaction studies have not been conducted with CIMZIA upon concomitant administration with corticosteroids, nonsteroidal anti-inflammatory drugs, analgesics or immunosupressants.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies of CIMZIA have not been conducted to assess its carcinogenic potential. Certolizumab pegol was not genotoxic in the Ames test, the human peripheral blood lymphocytes chromosomal aberration assay, or the mouse bone marrow micronucleus assay.

Since certolizumab pegol does not cross-react with mouse or rat TNFα, reproduction studies were performed in rats using a rodent anti-murine TNFα pegylated Fab fragment (cTN3 PF), similar to certolizumab pegol. The cTN3 PF had no effects on the fertility and general reproductive performance of male and female rats at intravenous doses up 100 mg/kg, administered twice weekly.

14 CLINICAL STUDIES

14.1 Crohn's Disease

The efficacy and safety of CIMZIA were assessed in two double-blind, randomized, placebo-controlled studies in patients aged 18 years and older with moderately to severely active Crohn's disease, as defined by a Crohn's Disease Activity Index (CDAI[1]) of 220 to 450 points, inclusive. CIMZIA was administered subcutaneously at a dose of 400 mg in both studies. Stable concomitant medications for Crohn's disease were permitted.

Study CD1

Study CD1 was a randomized placebo-controlled study in 662 patients with active Crohn's disease. CIMZIA or placebo was administered at Weeks 0, 2, and 4 and then every four weeks to Week 24. Assessments were done at Weeks 6 and 26. Clinical response was defined as at least a 100-point reduction in CDAI score compared to baseline, and clinical remission was defined as an absolute CDAI score of 150 points or lower.

The results for Study CD1 are provided in Table 2. At Week 6, the proportion of clinical responders was statistically significantly greater for CIMZIA-treated patients compared to controls. The difference in clinical remission rates was not statistically significant at Week 6. The difference in the proportion of patients who were in clinical response at both Weeks 6 and 26 was also statistically significant, demonstrating maintenance of clinical response.

Table 2 Study CD1 – Clinical Response and Remission, Overall Study Population

Timepoint	% Response or Remission (95% CI)	
	Placebo (N = 328)	CIMZIA 400 mg (N = 331)
Week 6		
Clinical Response[#]	**27%** (22%, 32%)	**35%** (30%, 40%)*
Clinical Remission[#]	**17%** (13%, 22%)	**22%** (17%, 26%)
Week 26		
Clinical Response	**27%** (22%, 31%)	**37%** (32%, 42%)*
Clinical Remission	**18%** (14%, 22%)	**29%** (25%, 34%)*
Both Weeks 6 & 26		
Clinical Response	**16%** (12%, 20%)	**23%** (18%, 28%)*
Clinical Remission	**10%** (7%, 13%)	**14%** (11%, 18%)

* p-value < 0.05 logistic regression test
[#] Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points

Study CD2

Study CD2 was a randomized treatment-withdrawal study in patients with active Crohn's disease. All patients who entered the study were dosed initially with CIMZIA 400 mg at Weeks 0, 2, and 4 and then assessed for clinical response at Week 6 (as defined by at least a 100-point reduction in CDAI score). At Week 6, a group of 428 clinical responders was randomized to receive either CIMZIA 400 mg or placebo, every four weeks starting at Week 8, as maintenance therapy through Week 24. Non-responders at Week 6 were withdrawn from the study. Final evaluation was based on the CDAI score at Week 26. Patients who withdrew or who received rescue therapy were considered not to be in clinical response. Three randomized responders received no study injections, and were excluded from the ITT analysis.

The results for clinical response and remission are shown in Table 3. At Week 26, a statistically significantly greater proportion of Week 6 responders were in clinical response and in clinical remission in the CIMZIA-treated group compared to the group treated with placebo.

Table 3 Study CD2 - Clinical Response and Clinical Remission

	% Response or Remission (95% CI)	
	CIMZIA 400 mg x3 + Placebo N = 210	**CIMZIA 400 mg N = 215**
Week 26		
Clinical Response[#]	**36%** (30%, 43%)	**63%** (56%, 69%)*
Clinical Remission[#]	**29%** (22%, 35%)	**48%** (41%, 55%)*

* $p < 0.05$
[#] Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points

Baseline use of immunosuppressants or corticosteroids had no impact on the clinical response to CIMZIA.

14.2 Rheumatoid Arthritis

The efficacy and safety of CIMZIA were assessed in four randomized, placebo-controlled, double-blind studies (RA-I, RA-II, RA-III, and RA-IV) in patients ≥ 18 years of age with moderately to severely active rheumatoid arthritis diagnosed according to the American College of Rheumatology (ACR) criteria. Patients had ≥ 9 swollen and tender joints and had active RA for at least 6 months prior to baseline. CIMZIA was administered subcutaneously in combination with MTX at stable doses of at least 10 mg weekly in Studies RA-I, RA-II, and RA-III. CIMZIA was administered as monotherapy in Study RA-IV.

Study RA-I and Study RA-II evaluated patients who had received MTX for at least 6 months prior to study medication, but had an incomplete response to MTX alone. Patients were treated with a loading dose of 400 mg at Weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either 200 mg or 400 mg of CIMZIA or placebo every other week, in combination with MTX for 52 weeks in Study RA-I and for 24 weeks in Study RA-II. Patients were evaluated for signs and symptoms and structural damage using the ACR20 response at Week 24 (RA-I and RA-II) and modified Total Sharp Score (mTSS) at Week 52 (RA-I). The open-label extension follow-up study enrolled 846 patients who received 400 mg of CIMZIA every other week.

Study RA-III evaluated 247 patients who had active disease despite receiving MTX for at least 6 months prior to study enrollment. Patients received 400 mg of CIMZIA every four weeks for 24 weeks without a prior loading dose. Patients were evaluated for signs and symptoms of RA using the ACR20 at Week 24.

Study RA-IV (monotherapy) evaluated 220 patients who had failed at least one DMARD use prior to receiving CIMZIA. Patients were treated with CIMZIA 400 mg or placebo every 4 weeks for 24 weeks. Patients were evaluated for signs and symptoms of active RA using the ACR20 at Week 24.

Clinical Response

The percent of CIMZIA-treated patients achieving ACR20, 50, and 70 responses in Studies RA-I and RA-IV are shown in Table 4. CIMZIA-treated patients had higher ACR20, 50 and 70 response rates at 6 months compared to placebo-treated patients. The results in study RA-II (619 patients) were similar to the results in RA-I at Week 24. The results in study RA-III (247 patients)

were similar to those seen in study RA-IV. Over the one-year Study RA-I, 13% of CIMZIA-treated patients achieved a major clinical response, defined as achieving an ACR70 response over a continuous 6-month period, compared to 1% of placebo-treated patients.

Table 4: ACR Responses in Studies RA-I, and RA-IV (Percent of Patients)

Response	Study RA-I Methotrexate Combination (24 and 52 weeks)			Study RA-IV Monotherapy (24 weeks)		
	Placebo + MTX N=199	CIMZIA[a] 200 mg + MTX q 2 weeks N=393	CIMZIA[a] 200 mg + MTX - Placebo + MTX (95% CI)[d]	Placebo N=109	CIMZIA[b] 400 mg q 4 weeks N=111	CIMZIA[b] 400 mg - Placebo (95% CI)[d]
ACR20						
Week 24	14%	59%	45% (38%, 52%)	9%	46%	36% (25%, 47%)
Week 52	13%	53%	40% (33%, 47%)	N/A	N/A	
ACR50						
Week 24	8%	37%	30% (24%, 36%)	4%	23%	19% (10%, 28%)
Week 52	8%	38%	30% (24%, 37%)	N/A	N/A	
ACR70						
Week 24	3%	21%	18% (14%, 23%)	0%	6%	6% (1%, 10%)
Week 52	4%	21%	18% (13%, 22%)	N/A	N/A	
Major Clinical Response[c]	1%	13%	12% (8%, 15%)			

[a] CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
[b] CIMZIA administered every 4 weeks not preceded by a loading dose regimen
[c] Major clinical response is defined as achieving ACR70 response over a continuous 6-month period
[d] 95% Confidence Intervals constructed using the large sample approximation to the Normal Distribution.

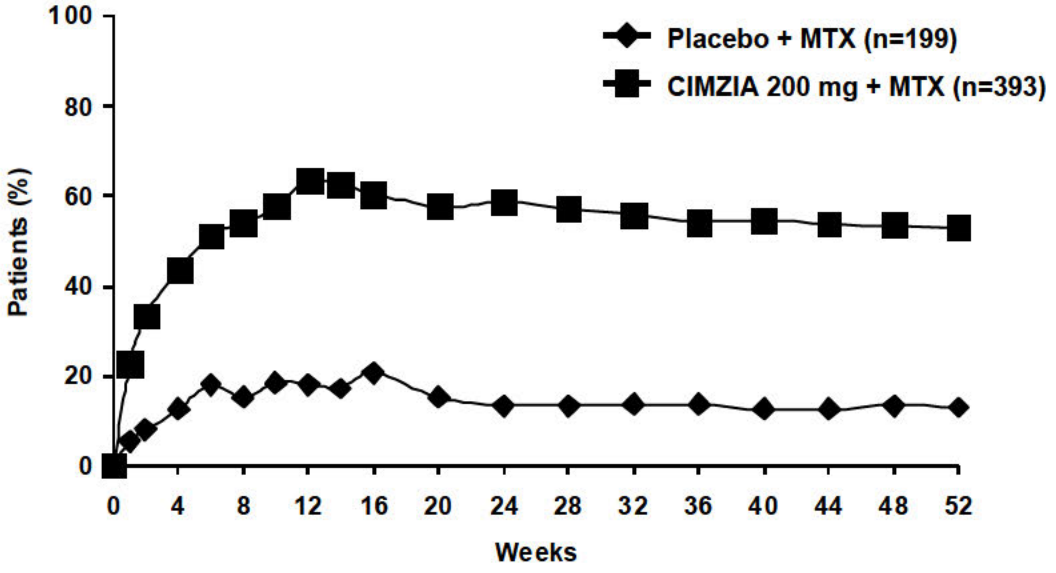
Table 5: Components of ACR Response in Studies RA-I and RA-IV

Parameter+	Study RA-I				Study RA-IV			
	Placebo + MTX N=199		CIMZIA(a) 200 mg + MTX q 2 weeks N=393		Placebo + MTX N=109		CIMZIA(b) 400 mg q 4 weeks Monotherapy N=111	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
Number of tender joints (0-68)	28	27	29	9	28 (12.5)	24 (15.4)	30 (13.7)	16 (15.8)
Number of swollen joints (0-66)	20	19	20	4	20 (9.3)	16 (12.5)	21 (10.1)	12 (11.2)
Physician global assessment(c)	66	56	65	25	4 (0.6)	3 (1.0)	4 (0.7)	3 (1.1)
Patient global assessment(c)	67	60	64	32	3 (0.8)	3 (1.0)	3 (0.8)	3 (1.0)
Pain(c)(d)	65	60	65	32	55 (20.8)	60 (26.7)	58 (21.9)	39 (29.6)
Disability index (HAQ)(e)	1.75	1.63	1.75	1.00	1.55 (0.65)	1.62 (0.68)	1.43 (0.63)	1.04 (0.74)
CRP (mg/L)	16.0	14.0	16.0	4.0	11.3	13.5	11.6	6.4

(a) CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
(b) CIMZIA administered every 4 weeks not preceded by a loading dose regimen
(c) Study RA-I - Visual Analog Scale: 0 = best, 100 = worst. Study RA-IV - Five Point Scale: 1 = best, 5 = worst
(d) Patient Assessment of Arthritis Pain**.** Visual Analog Scale: 0=best, 100=worst
(e) Health Assessment Questionnaire Disability Index; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity
All values are last observation carried forward.
+For Study RA-I, median is presented. For Study RA-IV, mean (SD) is presented except for CRP which presents geometric mean

The percent of patients achieving ACR20 responses by visit for Study RA-I is shown in Figure 1. Among patients receiving CIMZIA, clinical responses were seen in some patients within one to two weeks after initiation of therapy.

Figure 1 Study RA-I ACR20 Response Over 52 Weeks*



*The same patients may not have responded at each time point

Radiographic Response

In Study RA-I, inhibition of progression of structural damage was assessed radiographically and expressed as the change in modified Total Sharp Score (mTSS) and its components, the Erosion Score (ES) and Joint Space Narrowing (JSN) score, at Week 52, compared to baseline. CIMZIA inhibited the progression of structural damage compared to placebo plus MTX after 12 months of treatment as shown in Table 6. In the placebo group, 52% of patients experienced no radiographic progression (mTSS $\leq$0.0) at Week 52 compared to 69% in the CIMZIA 200 mg every other week treatment group. Study RA-II showed similar results at Week 24.

Table 6: Radiographic Changes at 6 and 12 months in Study RA-I

	Placebo + MTX N=199 Mean (SD)	CIMZIA 200 mg + MTX N=393 Mean (SD)	CIMZIA 200 mg + MTX – Placebo + MTX Mean Difference
mTSS			
Baseline	40 (45)	38 (49)	--
Week 24	1.3 (3.8)	0.2 (3.2)	-1.1
Week 52	2.8 (7.8)	0.4 (5.7)	-2.4
Erosion Score			
Baseline	14 (21)	15 (24)	--
Week 24	0.7 (2.1)	0.0 (1.5)	-0.7
Week 52	1.5 (4.3)	0.1 (2.5)	-1.4
JSN Score			
Baseline	25 (27)	24 (28)	--
Week 24	0.7 (2.4)	0.2 (2.5)	-0.5
Week 52	1.4 (5.0)	0.4 (4.2)	-1.0

An ANCOVA was fitted to the ranked change from baseline for each measure with region and treatment as factors and rank baseline as a covariate.

Physical Function Response

In studies RA-I, RA-II, RA-III, and RA-IV, CIMZIA-treated patients achieved greater improvements from baseline than placebo-treated patients in physical function as assessed by the Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 24 (RA-II, RA-III and RA-IV) and at Week 52 (RA-I).

15 REFERENCES

1. Best WR, Becktel JM, Singleton JW, Kern F: Development of a Crohn's Disease Activity Index, National Cooperative Crohn's Disease Study. Gastroenterology 1976; 70(3): 439-444

16 HOW SUPPLIED/STORAGE AND HANDLING

Storage and Stability
Refrigerate intact carton at 2 to 8 °C (36 to 46 °F). Do not freeze. Do not separate contents of carton prior to use. Do not use beyond expiration date, which is located on the drug label and carton. Protect solution from light.

- **Lyophilized Powder for Reconstitution:**
  NDC 50474-700-62

  Pack Content

Qty.	Item
2	Type I glass vials with rubber stopper and overseals each containing 200 mg of lyophilized CIMZIA for reconstitution.
2	2 mL Type I glass vials containing 1 mL sterile Water for Injection
2	3 mL plastic syringes
4	20 gauge luer-lock needles (1 inch)
2	23 gauge luer-lock needles (1 inch)
8	Alcohol swabs

- **Prefilled Syringe**
  NDC 50474-710-79
  2 alcohol swabs and 2 single use prefilled glass syringes with a fixed 25 ½ gauge thin-wall needle, each containing 200 mg (1 mL) of CIMZIA.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.3).

17.1 Patient Counseling

Advise patients of the potential risks and benefits of CIMZIA therapy. Be sure that patients receive the Medication Guide and allow them time to read it prior to starting CIMZIA therapy and to review it periodically. Any questions resulting from the patient's reading of the Medication Guide should be discussed. Because caution should be exercised in prescribing CIMZIA to patients with clinically important active infections, advise patients of the importance of informing their health care providers about all aspects of their health.

- **Immunosuppression**

Inform patients that CIMZIA may lower the ability of the immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis and reactivation of hepatitis B virus infections.

Counsel patients about the possible risk of lymphoma and other malignancies while receiving CIMZIA.

- **Allergic Reactions**

Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. The prefilled syringe components do not contain any latex or dry natural rubber.

- **Other Medical Conditions**

Advise patients to report any signs of new or worsening medical conditions such as heart disease, neurological disease, or autoimmune disorders. Advise patients to report promptly any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

17.2 Instruction on Prefilled Syringe Self-Injection Technique

In the event that the patient or caregiver is giving the CIMZIA injection, they need to be instructed by a qualified healthcare professional in proper injection technique, and their ability to administer CIMZIA subcutaneous injections should be checked to ensure correct administration. Suitable sites for injection include the thigh or abdomen. CIMZIA should be injected when the liquid is at room temperature *[see FDA-approved Medication Guide (17.3)]*

To avoid needle-stick injury, patients and healthcare providers should not attempt to place the needle cover back on the syringe or otherwise recap the needle. Be sure to properly dispose of needles and syringes in a puncture-proof container, and instruct patients and caregivers in proper syringe and needle disposal technique. Actively discourage any reuse of the injection materials.

17.3 Medication Guide

MEDICATION GUIDE
CIMZIA® (CIM-zee-uh)
(certolizumab pegol)

Read the Medication Guide that comes with CIMZIA before you start using it, and before each injection of CIMZIA. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about CIMZIA?

CIMZIA is a medicine that affects your immune system. CIMZIA can lower the ability of the immune system to fight infections. Serious infections have happened in patients taking CIMZIA. These infections include tuberculosis (TB) and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some patients have died from these infections.

- Your doctor should test you for TB before starting CIMZIA.
- Your doctor should monitor you closely for signs and symptoms of TB during treatment with CIMZIA.

Before starting CIMZIA, tell your doctor if you:

- think you have an infection. You should not start taking CIMZIA if you have any kind of infection.
- are being treated for an infection
- have signs of an infection, such as a fever, cough, flu-like symptoms
- have any open cuts or sores on your body
- get a lot of infections or have infections that keep coming back
- have diabetes
- have HIV
- have tuberculosis (TB), or have been in close contact with someone with TB
- were born in, lived in, or traveled to countries where there is more risk for getting TB. Ask your doctor if you are not sure.
- live or have lived in certain parts of the country (such as the Ohio and Mississippi River valleys) where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis). These infections may develop or become more severe if you take CIMZIA. If you do not know if you have lived in an area where histoplasmosis, coccidioidomycosis, or blastomycosis is common, ask your doctor.
- have or have had hepatitis B
- use the medicine Kineret® (anakinra), Orencia® (abatacept), Rituxan® (rituximab), or Tysabri® (natalizumab)

After starting CIMZIA, if you get an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have open cuts or sores on your body, call your doctor right away. CIMZIA can make you more likely to get infections or make any infection that you may have worse.

What is CIMZIA?
CIMZIA is a medicine called a Tumor Necrosis Factor (TNF) blocker. CIMZIA is used in adult patients to:

- Lessen the signs and symptoms of moderately to severely active Crohn's disease (CD) in adults who have not been helped enough by usual treatments.
- Treat moderately to severely active rheumatoid arthritis (RA).

It is not known whether CIMZIA is safe and effective in children.

What should I tell my doctor before starting treatment with CIMZIA?
CIMZIA may not be right for you. Before starting CIMZIA, tell your doctor about all of your medical conditions, including if you:

- **have an infection.** (See, 'What is the most important information I should know about CIMZIA?")
- **have or have had any type of cancer.**
- **have congestive heart failure.**
- **have seizures, any numbness or tingling, or a disease that affects your nervous system such as multiple sclerosis.**
- **are scheduled to receive a vaccine.** Do not receive a live vaccine while taking CIMZIA.
- **are allergic to any of the ingredients in CIMZIA.** See the end of this Medication Guide for a list of the ingredients in CIMZIA.

Tell your doctor if you are pregnant, planning to become pregnant, or breastfeeding. CIMZIA has not been studied in pregnant or nursing women.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Your doctor will tell you if it is okay to take your other medicines while taking CIMZIA. Especially, tell your doctor if you take:

- Kineret® (anakinra), Orencia® (abatacept), Rituxan® (rituximab), Tysabri® (natalizumab). You have a higher chance for serious infections when taking CIMZIA with Kineret®, Orencia®, Rituxan®, or Tysabri®.
- A TNF blocker: Remicade® (infliximab), Humira® (adalimumab), Enbrel® (etanercept).

You should not take CIMZIA while you take one of these medicines.

How should I use CIMZIA?
Lyophilized Powder for Reconstitution:

- If your doctor prescribes the CIMZIA lyophilized pack, CIMZIA should be injected by a healthcare provider. Each dose of CIMZIA will be given as two separate injections under the skin in your stomach area (abdomen) or upper leg (thigh).

- Make sure to keep all of your injection and follow-up appointments with your doctor.

Prefilled Syringe:

- If your doctor prescribes the CIMZIA prefilled syringe, see the section **"Patient Instructions for Use"** at the end of the Medication Guide for complete instructions for use.

- Do not give yourself an injection of CIMZIA unless you have been shown by your doctor or nurse. Call your doctor if you have questions. Someone you know can also help you with your injection after they have been trained by your doctor or nurse.

- CIMZIA is given by an injection under the skin. Your doctor will tell you how much CIMZIA to inject and how often to inject CIMZIA, based on your condition to be treated. Do not use more CIMZIA or inject more often than prescribed.

- Depending on the amount of CIMZIA prescribed by your doctor, you may need more than one injection at a time.

- If you are prescribed to take 400 mg of CIMZIA, you will need two injections. You will need to use two CIMZIA prefilled syringes.

- CIMZIA may be injected into your abdomen or thigh area. If you are prescribed to have more than one injection, each injection should be given at a different site in your abdomen or thigh.

- Make sure the solution in the prefilled syringe is clear and colorless to light yellow. The solution should be essentially free from particles. **Do not use the CIMZIA prefilled syringe if the medicine looks cloudy or if there are large or colored particles.**

- Do not miss any doses of CIMZIA. If you forget to take CIMZIA, inject a dose as soon as you remember. Then, take your next dose at your regularly scheduled time.

- Make sure to keep all follow-up appointments with your doctor.

What are the possible side effects of CIMZIA?
Serious side effects have happened in patients taking CIMZIA including:

- **Serious infections including TB.** See "**What is the most important information I should know about CIMZIA?**"
- **Certain Types of Cancer.** There have been cases of certain types of cancer in people taking CIMZIA or other TNF blockers. People with RA, especially more serious RA, may have a higher chance for getting a kind of cancer called lymphoma.
- **Heart Failure** including new heart failure or worsening of heart failure you already have. Symptoms include shortness of breath, swelling of your ankles or feet, or sudden weight gain.
- **Nervous System Problems** such as multiple sclerosis, seizures, or inflammation of the nerves of the eyes. Symptoms include dizziness, numbness or tingling, problems with your vision, and weakness in your arms or legs.
- **Allergic Reactions.** Signs of an allergic reaction include a skin rash, swelling of the face, tongue, lips, or throat, or trouble breathing.

- **Hepatitis B virus reactivation in patients who carry the virus in their blood.** In some cases patients have died as a result of hepatitis B virus being reactivated. Your doctor should monitor you carefully during treatment with CIMZIA if you carry the hepatitis B virus in your blood. Tell your doctor if you have any of the following symptoms:

  - feel unwell
  - poor appetite
  - tiredness (fatigue)
  - fever, skin rash, or joint pain

- **Blood Problems.** Your body may not make enough of the blood cells that help fight infections or help stop bleeding. Symptoms include a fever that doesn't go away, bruising or bleeding very easily, or looking very pale.
- **Immune reactions including a lupus-like syndrome.** Symptoms include shortness of breath, joint pain, or a rash on the cheeks or arms that worsens with sun exposure.

Call your doctor right away if you develop any of the above side effects or symptoms.

The most common side effects in people taking CIMZIA are:

- upper respiratory infections (flu, cold)
- rash
- urinary tract infections (bladder infections)

Injection site reactions such as redness, rash, swelling, itching or bruising can happen in some people. These symptoms will usually go away within a few days. If you have pain, redness, or swelling around the injection site that doesn't go away within a few days or gets worse, call your doctor right away.

Tell your doctor about any side effect that bothers you or does not go away.

These are not all of the side effects with CIMZIA. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about CIMZIA
Medicines are sometimes prescribed for purposes that are not mentioned in Medication Guides. Do not use CIMZIA for a condition for which it was not prescribed. Do not give CIMZIA to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about CIMZIA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about CIMZIA that is written for health professionals.

For more information go to www.CIMZIA.com or you can enroll in a patient support program by calling 1-866-4CIMZIA (424-6942).

How should I store CIMZIA?

- Keep CIMZIA in the refrigerator at 36ºF – 46ºF (2ºC – 8ºC)
- Let CIMZIA to come to room temperature before injecting it.
- **Do not freeze** CIMZIA.
- **Protect** CIMZIA **from light.** Store CIMZIA in the carton.
- Do not use CIMZIA if the medication is expired (today's date is past the date printed on the vial, prefilled syringe or carton), or if the liquid looks cloudy or discolored.

The vials and prefilled syringe are glass. Do not drop or crush them.

Always keep CIMZIA, injection supplies, puncture-proof container, and all other medicines out of the reach of children.

What are the ingredients in CIMZIA?
CIMZIA lyophilized powder:
Active ingredient: certolizumab pegol.

Inactive ingredients: sucrose, lactic acid, polysorbate.
The pack contains Water for Injection, for reconstitution of the lyophilized powder.

CIMZIA prefilled syringe:
Active ingredient: certolizumab pegol
Inactive ingredients: sodium acetate, sodium chloride, and Water for Injection.
CIMZIA has no preservatives.

Patient Instructions for Use
The instructions below are only to be used with CIMZIA in Prefilled Syringes.

What do I need to do to prepare and give an injection of CIMZIA?

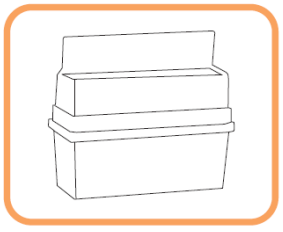
Do not use the CIMZIA prefilled syringe if:

- any name other than "CIMZIA" is on the package and prefilled syringe label
- the expiration date on the container has passed
- the packaging is torn or if the tamper evident seals are missing or broken on the top and bottom of carton when you receive it. If this is the case, contact your pharmacist
- the prefilled syringe is frozen or has been left in direct sunlight
- the medicine in the prefilled syringe is not clear to pale yellow, or has large, colored particles in it.

Preparing to use the CIMZIA prefilled syringe

Each CIMZIA prefilled syringe package comes with these items in a tray:
- 2 glass prefilled syringes of CIMZIA. Each has a fixed needle.
- 2 alcohol swabs

For each injection you will use-
- 1 prefilled syringe of CIMZIA with needle
- 1 alcohol swab



For each injection you will also need:
- 1 clean cotton ball or gauze pads. These are not included in CIMZIA prefilled syringe package.
- a puncture-proof container for disposing of used needles and syringes. (See the section entitled "How do I dispose of needles and syringes?")

If you do not have all the supplies you need, talk to your pharmacist.
- Each prefilled syringe contains the right dose of medicine for one injection (200 mg).

- Depending on the amount of CIMZIA prescribed by your doctor, you may need to take more than one injection.

- If you are prescribed to take 400 mg of CIMZIA, you will need to take two injections. You will need to use two CIMZIA prefilled syringes.

- CIMZIA may be injected into your abdomen or thigh area. If you are prescribed to take more than one injection, each injection should be given at a different injection site, in your abdomen and thigh.

1. Take either one or two CIMZIA prefilled syringes and alcohol swabs out of the refrigerator for injection, depending on your prescribed dose. If there is still a prefilled syringe in the carton, put it back in the refrigerator right away. If both prefilled syringes are used, throw away the empty carton after you finish your injection.

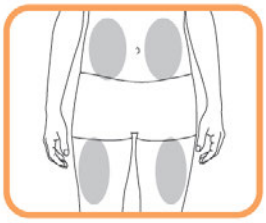
2. Let the medicine in the syringe come to room temperature before injection. This will take about 30 minutes.

For your protection, it's important that you carefully follow these instructions:

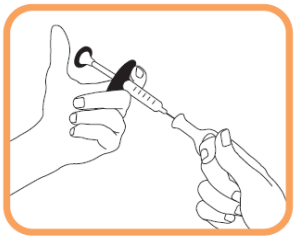
Choosing and preparing an injection site

3. Wash your hands thoroughly.

4. Choose a different site on your abdomen or thigh for each injection. Each new injection should be given at least one inch from a site you used before. If you choose the abdomen, avoid the 2 inches around your navel. Do not inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks. Change injection sites between your abdomen and thighs to reduce the risk of reaction. You may find it helpful to keep notes on the locations of injection sites you use.

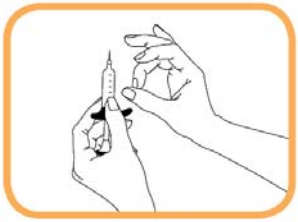


5. Use an alcohol swab to wipe over the site where you will inject CIMZIA. Do not touch the clean area again until you are ready for the injection.

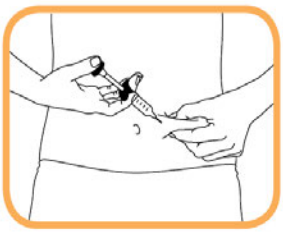


Using the CIMZIA prefilled syringe

6. Remove the needle cover by pulling straight up on the plastic ring. Take care not to touch the needle and do not allow the needle to touch any surface. Place the needle cover to the side.

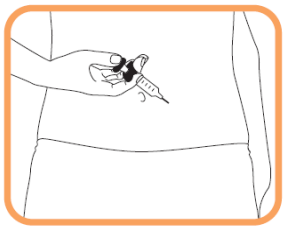


7. Hold the syringe so the needle is pointing up. Lightly tap the syringe to push any air bubbles to the top. Push the plunger slowly to remove any bubbles. Stop pushing the plunger once all of the air bubbles are gone. If a small drop of liquid comes out of the needle that is okay.



8. Hold the syringe with the needle facing down. Do not touch the needle with your fingers or let it touch any surface.

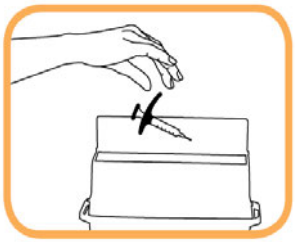
9. Hold the syringe in one hand. Use the other hand to gently pinch a fold of cleaned area of skin. Insert the needle at about a 45 degree angle with a quick, short, "dart-like" motion.



10. Release the skin pinch, keeping the syringe in position. Pull back slowly on the plunger. If blood enters the syringe, this means you have entered a blood vessel. Do not inject CIMZIA. Pull the needle out and throw away the prefilled syringe and needle in a puncture-proof container. Repeat the steps to prepare for an injection using a new prefilled syringe. **Do not use the same prefilled syringe.**

11. If no blood appears, inject all of the medicine in the prefilled syringe under the skin.

12. When the syringe is empty, remove the needle from the skin and press the clean cotton ball or gauze pad over the injection site for ten seconds. Do not rub the injection site. You may have a slight amount of bleeding. This is normal.



13. To avoid needle-stick injury, do not try to recap the needle. Throw away the used prefilled syringe and needle in a special puncture-proof container (**see the section entitled "How should I dispose of needles and syringes?")**

14. Repeat steps 5-13 above if you are prescribed to take a second injection of CIMZIA (total 400 mg dose).

How should I throw away (dispose of) needles and syringes?
To avoid needle-stick injury, do not try to recap the needle. Before you start injecting CIMZIA at home, check with your doctor for instructions on the right way to throw away your used needles and used prefilled syringes. There may be special state or local laws about throwing away used needles and syringes.

Ask your doctor or pharmacist about how to get a puncture-proof container ("sharps" container) that will meet the requirements of your particular state or town.

When the container is about two-thirds full, tape the lid closed. Dispose of the container as instructed by your doctor, nurse or pharmacist. Do not throw away the container in the trash or recycle.

Alcohol swabs may be placed in the trash, unless you are instructed otherwise.

Always keep CIMZIA, injection supplies, puncture-proof container, and all other medicines out of the reach of children.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Product developed and manufactured for:
UCB, Inc.
1950 Lake Park Drive
Smyrna, GA 30080

US License No. 1736

Revised 05/ 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

REMS

CIMZIA®
BLA 125160/125271

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

1. GOAL

Goal: To communicate and mitigate the risks associated with CIMZIA® therapy by:

- Alerting and warning healthcare providers of the recent cases for unrecognized histoplasmosis and other invasive fungal infections associated with concomitant Tumor Necrosis Factor (TNF) blocker use.
- Educating patients of the associated risks with CIMZIA® therapy for serious infections including tuberculosis (TB) and infections caused by viruses, fungi, and bacteria spreading throughout the body.

2. REMS ELEMENTS

2.1 MEDICATION GUIDE

A Medication Guide (MG) will be dispensed with each CIMZIA® kit in accordance with 21 CFR 208.24. Each CIMZIA® kit contains the product's approved package insert (labeling) along with the MG.

If a CIMZIA® kit containing the lyophilized powder for reconstitution with diluent, needles, and swabs, is distributed to be administered by a healthcare professional, the MG will be provided by the healthcare professional, and additional MGs will be provided by UCB Medical Science Liaisons (MSLs) and sales representatives to healthcare providers if necessary.

Please see the appended Medication Guide.

2.2 COMMUNICATION PLAN

In accordance to FDCA 505-1(e)(3), UCB will implement a communication plan to healthcare professionals (HCPs), including in particular, gastroenterologists, rheumatologists, and current TNF blocker prescribers, that conveys the following information:

- The risk of developing invasive fungal infections, including histoplasmosis, coccidioidomycosis, blastomycosis, and other opportunistic fungal infections while treating with TNF blockers.

- Provide descriptive information on the signs and symptoms of fungal infections, including histoplasmosis.
- Provide references and background information regarding the treatment of these infections.

The purpose of the communication plan is to establish the REMS in the healthcare community and communicate new safety information. This element of the REMS is not intended to continue over the lifetime of the product; it will function only to disseminate the new safety information about histoplasmosis and fungal infections.

The communication plan includes a *Dear Healthcare Provider Letter*, web-based materials to inform healthcare providers and patients, and a Medical Scientific Liaison slide deck.

2.2.1 Dear Healthcare Provider Letter

UCB will issue a Dear Healthcare Provider Letter to targeted healthcare providers within 60 days of the REMS approval. The purpose of the letter is to inform healthcare providers of the risk of developing invasive fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, and other opportunistic fungal infections while on treatment with TNFα blockers, the signs and symptoms of possible systemic fungal infections, the need to suspect fungal infection in symptomatic patients who live or travel to endemic regions, and the need to reevaluate the benefit/risk prior to restarting TNFα blocker therapy after recovery from a fungal infection. In addition, the letter provides healthcare providers with information to discuss with their patients.

UCB will disseminate the Dear Healthcare Provider Letters through First Class U.S. mail and target U.S. healthcare providers in the following specialties: gastroenterology, rheumatology, internal medicine, family medicine, emergency medicine, and infectious disease specialists in the endemic areas of the Ohio and Mississippi River valleys and San Joaquin valley.

Please see the appended Dear Healthcare Provider Letter.

2.2.2 Web-based Materials to Inform Healthcare Providers and Patients

UCB will develop a stand-alone link on the existing www.CIMZIA.com website entitled, "Important Safety Information Regarding Fungal Infections," within 60 days of the REMS approval. This link will direct users to a separate website that introduces the REMS program to providers and patients, while providing a copy of the Dear Healthcare Provider letter, approved Medication Guide, approved Package Insert, and approved Medical Science Liaison (MSL) slide deck. The website will also provide a brief summary describing the occurrence of histoplasmosis and other fungal infections.

The UCB CIMZIA.com website will be available to all healthcare providers as it is in the public domain and UCB sales representatives and MSLs will encourage healthcare providers to visit the information. Please see appended web-based materials.

2.2.3 Medical Scientific Liaison Slide Decks (Safety-related)

A specific dedicated slide deck to inform healthcare providers about the occurrence of unrecognized histoplasmosis and other invasive fungal infections in patients at risk will be presented to all Gastroenterology Key Opinion Leaders (approximately 500) and Rheumatology Key Opinion Leaders (approximately 600).
Please see appended slide deck.

3. TIMETABLE FOR ASSESSMENTS

UCB will submit a REMS Assessment to FDA at the following timetables:

1st FDAAA Assessment:	November 2009
2nd FDAAA Assessment:	May 2011
3rd FDAAA Assessment:	May 2015

UCB is required to submit assessments within 60 days of the noted time intervals.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

SUMMARY REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

MAY 13 2009

Summary Review for Regulatory Action

Date	May 13, 2009
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
BLA #	125271
Applicant Name	UCB Pharma, Inc.
Date of Submission	March 13, 2009
PDUFA Goal Date	May 13, 2009
Proprietary Name / Established (USAN) Name	Cimzia Certolizumab Pegol
Dosage Forms / Strength	Sterile parenteral solution, 200 mg/mL in pre-filled syringe for subcutaneous injection
Proposed Indication	For the treatment of patients with rheumatoid arthritis
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Carolyn L. Yancey, M.D.; Jane L. Gilbert, M.D., Ph.D.
Statistical Review	Kate Meaker, M.S.; Dionne Price, Ph.D.
Pharmacology Toxicology Review	Gary P. Bond, Ph.D.; Adam Wasserman, Ph.D.
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Microbiology Review	N/A
Clinical Pharmacology Review	Srikanth C. Nallani, Ph.D.; Christopher W. Tornoe,Ph.D.; Jogarao Gobburu, Ph.D.; Suresh Doddapaneni, Ph.D.
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DEPI	Sigal Kaplan, Ph.D., B.Pharm/Pharmacoepidemiologist

OND=Office of New Drugs
DMIHP=Division of Medical Imaging and Hematology Products
DCRP=Division of Cardiovascular and Renal Products
SEALD=Study Endpoints and Labeling Development
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DMEPA=Division of Medication Error Prevention and Analysis
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The original supplementary BLA requesting addition of the Rheumatoid Arthritis (RA) indication to the Cimzia labeling was submitted on December 6, 2007. The division issued a Complete Response (CR) letter on January 2, 2009 based on our concerns regarding a possible cardiovascular toxicity signal focusing primarily on the higher incidence of cardiovascular deaths in the Cimzia arm compared to the placebo arm. My review of the original application explicates the findings of efficacy, safety and product quality for this product and has been appended to this document. This review will focus solely on the additional evaluations undertaken by the division regarding the cardiovascular (CV) safety concerns and the applicant's response to those concerns as defined in the CR letter. I will summarize the division's position on the cardiovascular safety of Cimizia for use in the RA patient population based on the applicant's complete response to the CR letter, the consult we obtained from the Division of Cardiovascular and Renal Products (DCRP), and the excellent review of the applicant's response and the DCRP consult written by Drs. Gilbert and Siegel.

After the CR letter was issued, the division consulted DCRP. The DCRP reviewers provided the following conclusions and recommendations based upon the data submitted in the supplement:

1. While the incidence of CV deaths was higher in the Cimzia-treated subjects compared to the placebo-treated subjects, when analyzed by Patient Exposure Years (PEY), the relative risk drops from 2.2 to 0.9. Two of the seven deaths attributed to CV adverse events may well have been primarily due to infection. Therefore, the true relative risk could favor either Cimzia or placebo. No additional restrictions on use or additional monitoring requirements are necessary.

2. As CV deaths usually occur in the setting of non-fatal CV adverse events, Dr. Marciniak also assessed the incidence of these events in the controlled periods of the Phase 3 studies. Here, he noted a higher incidence of heart failure, atrial fibrillation, hypertension, stroke/TIA and venous thrombosis/phlebitis in the Cimizia-treated subjects. He added that heart failure is a known risk associated with the TNF blockers and has been adequately addressed in the proposed label, but further evaluation of the hypertensive effect is warranted. He also recommended examining the rates of atrial fibrillation and strokes compared to the other TNF blockers when used in RA studies and in older patients, but did not recommend any additional monitoring to address these events.

The sponsor was granted a Post-Action Meeting which took place on February 3, 2009. Based on the DCRP consult, five questions were posed to the sponsor at that meeting. These questions asked the sponsor to more fully elucidate the adverse events of Congestive Heart Failure/Cardiomyopathy, Tachyarrhythmia/Tachycardia, Stroke/TIA, Hypertensive Events and Venous Thrombosis/Phlebitis. The sponsor then submitted their complete response to the CR letter on March 13, 2009 and the division determined at that time that that this response constituted a Type I complete response.

Drs. Gilbert and Siegel have completed a thorough review of the complete response. They have provided the following conclusions and recommendations:

1. Congestive Heart Failure/Cardiomyopathy: The sponsor's analysis is consistent with the FDA analyses. While there may be a small increased risk of worsening heart failure and cardiomyopathy associated with exposure to Cimzia, the risk is consistent with that seen with the other TNF blockers and is adequately addressed in the proposed product labeling.

2. Tachyarrhythmia/Tachycardia: The sponsor's analysis is consistent with the FDA analyses. There is a small risk of tachyarrhythmia and atrial fibrillation associated with exposure to Cimzia although that risk is twice that seen in the placebo subjects. The sponsor's proposed modifications to the product labeling are adequate to address this risk.

3. Stroke/TIA: Though there were a small number of events in the Cimzia-treated subjects, the incidence is twice as high in the placebo-treated subjects. The labeling must be modified to document this risk.

4. Hypertension: The incidence of hypertensive events is clearly higher in the Cimzia-treated subjects compared to the placebo-treated subjects and is exacerbated when there is a previous history of hypertension and when concomitant NSAIDs or corticosteroids are used. These data suggest careful use of Cimzia in patients with a history of hypertension and careful concomitant use of NSAIDs and corticosteroids. However, the risk of hypertensive events exists even without a history of hypertension or concomitant medication use and, therefore, the proposed labeling must be modified to reflect all of these risks.

5. Venous Thrombosis/Phlebitis: The sponsor's analyses are consistent with the FDA analyses. There appears to be a small increase in events in the Cimzia-treated subjects compared to the placebo-treated subjects. The sponsor's proposed modifications to the product labeling are adequate to address this concern.

In a follow-up consult after review of the sponsor's complete response, Dr. Marciniak added the following recommendation:

"We disagree with the sponsor's conclusion that "there is no apparent clinically relevant risk for HTN associated with Cimzia use." There is a possible risk that is poorly characterized. Most helpful would be a careful study of BP changes throughout the interdosing interval and with long term follow-up. Whether and when to require such a study is your decision."

In addenda to their initial reviews after evaluating the sponsor's complete response and Dr. Marciniak's follow-up consult, in addition to the labeling changes Drs. Gilbert and Siegel recommend a post-marketing requirement to establish a mechanism to evaluate these potentially serious CV events. While Dr. Gilbert suggested that, if feasible, an actual post-

marketing study would be the most productive option, Dr. Siegel concluded that these goals could be accomplished by incorporating appropriate assessments into the registry asked for by the Office of Safety and Epidemiology (OSE). (During the review of the original submission, OSE noted that a post-marketing registry should be conducted to collect safety data on patients receiving Cimzia. They recommended that such a registry be conducted under a PMR. In his memorandum of December 22, 2008, Dr. Siegel concurred that such a registry is a reasonable additional tool to further characterize the safety of Cimzia.) While I agree with Drs. Marciniak and Gilbert that a study would be the ideal tool for assessing the hypertensive effect of Cimzia in RA patients, most drug products are approved with some adverse effect signals that are generally followed with post-marketing observational procedures (except in the case of the most serious types of adverse effects) and I do not think that the addition of a required post-marketing study is warranted in this case. Therefore, I agree with Dr. Siegel's conclusion and recommendation regarding this matter.

- Regulatory Action

  Approval

- Risk Benefit Assessment

The sponsor has provided adequate evidence of the safety, efficacy and product quality to support approval of this application to extend the indication for Cimzia to the RA patient population. While certain CV safety concerns precluded approval on the first cycle, additional FDA and sponsor analyses have determined that these risks are relatively low, not greater than those seen with the other TNF-blocking agents, and can be adequately addressed by appropriate language in the product labeling and a postmarketing clinical study registry in adult patients with RA that would assess the longer term risks of these adverse events. This registry should, in particular, fully evaluate the hypertensive effects of Cimzia in RA patients.

- Recommendation for Postmarketing Risk Management Activities

This application has an approved REMS (Medication Guide) under BLA 125160. Because this application will become a supplement immediately following action, it will not have a separate REMS from the currently approved REMS under BLA 125160. On September 4, 2008, the Agency sent a supplement request letter to the Sponsor requesting a modification to the REMS. This modification included changes to the Medication Guide to incorporate new safety data regarding histoplasmosis and to create a Communication Plan. This labeling change was approved on December 22, 2008, and the Communication Plan was approved on December 31, 2008, under BLA 125160.

- Recommendation for Post-marketing Study Requirements

Post-marketing study requirements include the pediatric studies discussed in Section 10 of my initial review (see below), required under PREA and a post-marketing requirement to conduct a clinical study registry in adult patients with moderately to severely active RA that would assess the longer term risk for serious infections and malignancy that have been reported with TNFα blocker therapy as well as the longer term risk for congestive heart failure, TIA/stroke, tachyarrhythmia/atrial fibrillation, venous thrombosis/phlebitis and, in particular, hypertensive effects.

- Recommendation for Post-marketing Study Commitments

Dr. Rellahan recommended two post-marketing study commitments, which were agreed to by the Sponsor on December 24, 2008.

1. Re-evaluate the drug product sub-visible release and shelf-life specifications upon confirming the feasibility of a preparatory method that will enable implementation of the USP <788> preferred method. The data and specification assessment will be provided within two years from the time of approval.

Study Completion:	January 2011
Final Report Submission:	April 2011

2. Provide a commitment to conduct additional studies to evaluate the process-specific assay test for the assessment of HCP per your July 31, 2008 submission. A summary report and data will be provided by June 30, 2009.

Study Completion:	June 2009
Final Report Submission:	July 2009

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

JAN 2 2009

Summary Review for Regulatory Action

Date	January 2, 2009
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
BLA #	125271
Applicant Name	UCB Pharma, Inc.
Date of Submission	November 29, 2007
PDUFA Goal Date	January 2, 2009
Proprietary Name / Established (USAN) Name	Cimzia Certolizumab Pegol
Dosage Forms / Strength	Sterile parenteral solution, 200 mg/mL in pre-filled syringe for subcutaneous injection
Proposed Indication	For the treatment of patients with rheumatoid arthritis
Action:	Complete Response

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1. Introduction

Cimzia is a PEGylated monoclonal antibody Fab' fragment that binds to tumor necrosis factor-α (TNF-α) inhibiting the activity of this cytokine. It was developed by UCB Pharma. The sponsor initially submitted a BLA for Cimzia for the treatment of Crohn's disease and that application was approved in April of 2008. UCB submitted this application during the review period for the Crohn's disease application (BLA 125160), in support of an additional

indication, i.e., for the treatment of rheumatoid arthritis. Post-action, this BLA will administratively transfer to a supplemental application under BLA 125160. There have been three TNF-α inhibitor products previously licensed for the treatment of rheumatoid arthritis (RA). Of note, the approved formulation of Cimzia for Crohn's disease is a lyophilized powder for reconstitution and intravenous infusion, but the product under consideration for the RA indication is a sterile solution contained in a pre-filled syringe, for subcutaneous injection.

2. Background

While the application contains clear evidence to support the efficacy of Cimzia for the treatment of RA, a number of concerns were raised by the review team in regard to the product's safety profile and the product quality. (b) (4) [redacted]; however, additional information provided by the sponsor in response to the team's request appears to have provided adequate closure to this concern. Drs. Bond and Wasserman address this issue at length in their reviews. Immunogenicity concerns were raised by the clinical pharmacology review team and the clinical review team. These concerns relate to the choice of dosing regimen and the possibility of allowing an optional monotherapy regimen to be included in the product label. Additional concerns were related to possible product confusion due to the change in formulation from lyophilized powder to solution in pre-filled syringe as the two formulations will be concurrently marketed, and to questions regarding the need for a post-marketing safety registry and the choice of an appropriate pediatric development plan to satisfy the sponsor's responsibility under PREA. I will discuss each of these issues below in more detail.

3. CMC

This formulation of Cimzia has been changed, as noted above, from the lyophilized powder for reconstitution used for the Crohn's disease indication to a sterile solution in a pre-filled syringe. The CMC review team has recommended approval, concluding that the product is pure and potent, free from endogenous or adventitious infectious agents and that the manufacturing process results in a consistent product. They have determined that the data submitted in the application provide support for an 18-month dating period for Cimzia when the product is stored at 2 to 8° C, and that the dating period for the bulk drug substance should be (b) (4) [redacted] However, the DMEPA review team raised the possibility of administration errors occurring with the two different formulations available at the same time. Adequate resolution of that concern has been achieved as described in the comments from page 25 of Dr. Siegel's review:

> [*DMEPA*] was concerned that if [*patients*] with RA got a package with the lyophilized formulation that they would not know how to administer it. A teleconference was held with

the Applicant to discuss this issue and a proposal for resolution was discussed. (b) (4) (b) (4) [redacted]

On page 2 of her Quality Team Leader's Executive Summary, Dr. Rellahan states that two issues remain unresolved and will need to be addressed as post-marketing commitments (PMC):

1. Provide a commitment to re-evaluate the drug product sub visible particulates release and shelf-life specifications upon confirming the feasibility of a preparatory method that will enable implementation of the USP <788> preferred method.
2. Provide a commitment to conduct additional studies to evaluate the process-specific assay test for the assessment of HCP per your 31-Jul-08 submission. A summary report and data will be provided by 15 December 2008.

4. Nonclinical Pharmacology/Toxicology

As noted in Section 2 above, Drs. Bond and Wasserman expressed concern regarding the absence of adequate data to document the levels of the (b) (4) [redacted]. However, additional information was requested of the sponsor and received with adequate time for review. (b) (4) [redacted] Therefore, no PMCs or PMRs will be required to further assess this issue.

5. Clinical Pharmacology/Biopharmaceutics

The bioavailability of certolizumab with subcutaneous administration of Cimzia is approximately 80%. The following, reproduced from pages 6 and 7 of Dr. Siegel's review, summarizes the clinical pharmacology review team's conclusions and recommendations regarding the sponsor's proposed dosing regimens:

> Some patients receiving certolizumab pegol developed anti-product antibodies. Patients who developed anti-certolizumab antibodies had lower blood levels of certolizumab due to increased clearance and were less likely to have a clinical response. The likelihood of developing anti-certolizumab antibodies was increased in patients who received certolizumab monotherapy compared to patients receiving certolizumab in combination with methotrexate (MTX).
>
> Exposure-response modeling indicated that optimal ACR 20 responses were associated with trough certolizumab levels of 10 mcg/mL. The proposed load allows steady state levels to be achieved more quickly. The mean trough level for patients receiving the proposed dose

regimen exceeded the threshold of 10 mcg/mL; however, more patients achieved trough levels of 10 mcg/mL in the 400 mg q2wk arm than in the 200 mg q2wk arm. The proposed alternative dose regimen of 400 mg q4wk is associated with lower trough levels with exposure-response modeling, suggesting that the likelihood of achieving an ACR20 response is reduced from 70% to 50% with the q4w regimen as compared to the q2wk regimen. Based on the expectation of lower trough levels and predicted lower ACR20 responses with the q4wk regimen, and further lowering of certolizumab levels with monotherapy due to greater immunogenicity, the Clinical Pharmacology review team believes that the alternative 400 mg q4wk regimen is inappropriate for patients not receiving concomitant MTX. For labeling the review team suggests that the 400 q4wk regimen be recommended only for patients receiving concomitant MTX.

Dr. Siegel responds to this recommendation, on page 8 of his review:

Regarding the alternative 400 mg q4wk dose regimen, while it is true that efficacy for this regimen given as monotherapy is less than when it is given in combination with MTX, that regimen was tested and demonstrated to be efficacious (see Section 6, Clinical/Statistical below). Clinically, while TNF blockers are generally prescribed in combination with MTX, MTX does have serious toxicities associated with its use, including pulmonary toxicity, hematologic toxicity and liver toxicity so it would be important to offer to clinicians proven efficacious options for certolizumab use in patients who do not wish to take MTX or who cannot tolerate it. Rather than not offering the 400 mg q4wk regimen as an option for certolizumab monotherapy I would favor clearly communicating the increased risk of anti-certolizumab antibody formation and the lower level of efficacy shown with this alternative regimen.

I concur with Dr. Siegel's recommendation to include the monotherapy dosing regimen as an option for prescribers, as long as the labeling clearly describes the increased effectiveness seen when Cimzia is used in combination with MTX.

The clinical pharmacology review team evaluated the population pharmacokinetic data and identified body weight and antibody status as important covariates influencing clearance. Antibody status appeared to be the major contributor to variability in clearance. The team concluded that the influence of body weight was clinically insignificant. While no specific pharmacokinetic interactions were expected or seen between Cimzia and methotrexate (MTX), MTX co-administration did have an effect on certolizumab blood levels by reducing the likelihood of anti-certolizumab antibody formation.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

The sponsor submitted four clinical studies to support efficacy claims including the treatment of the signs and symptoms of RA, inhibition of progression of structural damage, improvement in physical function, and major clinical response. Based on an initial dose-finding study, a dosing regimen of 400 mg SC q4 weeks was employed in two of their Phase 3 trials. Study

011 was a randomized placebo-controlled, parallel-group, double-blind trial comparing Cimzia and placebo as monotherapy in patients with active RA. Study 014 was similar in design but compared Cimzia and placebo to patients on stable doses of MTX. The primary outcome analyses were comparisons of the proportions of subjects achieving an ACR20 at Week 24. The Tables below, reproduced from pages 9 and 10 of Dr. Siegel's review, summarize the results of those analyses:

Table 1: ACR20 Response at Week 24 – Study 011

ACR20 Response at Week 24 - Primary Analysis - Study 011 (mITT Population)			
	PBO N = 109	CZP 400 mg sc q4w N = 111	p-Value [a.]
Responder [b.]	10 (9%)	50 (46%)	<0.001

(a.) Cochran-Mantel-Haenszel (CMH) test of treatment comparison stratified by country.
(b.) A patient was considered a responder if he/she met the criteria of ACR20 improvement over Baseline at Week 24. Any patient who withdraws from the study at any time for any reason was considered a non-responder. Revised from sponsor Table 14.2.1:1, page 428 of 5470.

Table 2: Primary Endpoint Analysis and Sensitivity Analyses, ACR20 Response – Study 014

ACR20 Response at Week 24 - Study 014			
Sensitivity Analysis (mITT)			
	PBO + MTX N = 119	CZP 400 mg sc q4w + MTX N = 124	p-Value [a.]
Responder [b.]	32 (27%)	59 (48%)	<0.001
Sensitvity Analysis - Excuding Protocol Violators (mITT)			
Responder [b.]	21 (27%)	45 (50%)	0.002
Sensivity Analysis - Excluding CZP Treated Protocol Violators (mITT)			
Responder [b.]	27 (23%)	45 (50%)	<0.001

(a.) Cochran-Mantel-Haenszel (CMH) test of treatment comparison stratified by country.
(b.) A patient was considered a responder if he/she met the criteria for ACR20 improvement over Baseline at Week 24. Any patient who withdrew was considered a non-responder.
Abbreviations: PBO=placebo; MTX=methotrexate; mITT= modified intent-to-treat.
Revised from sponsor Table 14.2.1:2, page 443 of 6006.

However, as discussed in Dr. Siegel's review, the ACR50 and ACR70 responses on this dosing regimen were lower than have been seen with other products in this class. As this appeared to be a suboptimal dosing regimen, the sponsor used different regimens for subsequent studies.

Studies 027 and 050 were randomized, double-blind, placebo-controlled, parallel-arm trials comparing Cimzia, beginning with a loading dose of 400 mg SC q2 weeks times three doses followed by either 200 mg q2 weeks or 400 mg q2 weeks, to placebo in subjects with active RA on stable doses of MTX. The primary outcome endpoint was the proportion of subjects achieving an ACR20 at six months. Study 027 had an additional co-primary endpoint assessing radiographic disease progression using the change from baseline in the modified total Sharp score (mTSS). Multiplicity was controlled for by employing a sequential

approach, i.e., the mTSS results would only be analyzed if a statistically significant treatment effect was found in the analysis of the ACR20 outcome. The results of the primary analyses of the ACR20 responses from these two trials are summarized in the following tables reproduced from pages 15 and 16 of Dr. Siegel's review:

Table 3: Co-Primary ACR20 Response at Week 24 and Week 52 – Study 027

ACR Response - Study 027 (ITT Population)			
	PBO+ MTX N = 199	CZP 200 sc q2w + MTX N = 383	CZP 400 sc q2w + MTX N = 390
ACR-20			
Week 24			
n [c.]	198	388	388
Responder	27 (14%)	288 (59%)	236 (61%)
Odds ratio vs PBP+MTX [a.] (97.5% CI)		9 (5, 16)	10 (6, 17)
p-value		<0.001	<0.001
Week 52			
n [c.]	198	392	388
Responder	26 (13%)	208 (53%)	213 (55%)
Odds ratio vs PBO+MTX (95% CI) [b.]		8 (5, 12)	8 (5, 13)
ACR-50			
Week 24			
Responder	15 (8%)	144 (37%)	155 (40%)
Odds ratio vs PBO+MTX (95%CI) [b.]		8 (4, 13)	9 (5, 15)
p-value		<0.001	<0.001
Week 52			
Responder	15 (8%)	149 (38%)	155 (40%)
Odds ratio vs PBO+MTX (95%CI) [b.]		8 (4, 14)	8 (5, 5)
ACR-70			
Week 24			
Responder	6 (3%)	83 (21%)	80 (21%)
Odds ratio vs PBO+MTX (95%CI) [b.]		9 (3, 22)	8.7 (4, 21)
p-value		<0.001	<0.001
Week 52			
Responder	7 (4%)	83 (21%)	90 (23%)
Odds ratio vs PBO+MTX (95%CI) [b.]		8 (3, 17)	9 (4, 9)
p-value		<0.001	<0.001

Abbreviations: MTX=methotrexate; CI=confidence interval; PBO=placebo.
(a.) Odds ratio: CZP/PBO calculated using logistic regression with factors for treatment and region.
(b.) Wald p-values for the comparison of the treatment groups were calculated using logistic regression with factors for treatment and region.
(c.) n remains the same for calculation of the ACR-50 responses at Week 24 and Week 52, respectively.
Note: patients who withdrew or used rescue medication were considered as non-responders from that time-point forward. Revised from sponsor Table 11:11, page 105 of 8823.

Table 4: ACR-20, -50 and -70 Responses – Study 050

ACR Response - Study 050 (ITT Population) - Study 050			
	PBO + MTX N = 127	CZP 200 mg sc q2w + MTX N = 246	CZP 400 mg sc q2w + MTX N = 246
ACR-20 at Week 24			
n	127	246	245
Responder	11 (9%)	141 (57%)	141 (58%)
Odds ratio vs PBO + MTX [a.]		14	14
97.5% CI for odds ratio		[7, 31]	[7, 31]
p-value [c.]		<0.001	<0.001
Odds ratio vs CZP 200 mg q2w + MTX [b.]			1
95% CI for odds ratio			[1, 1]
p-value [c.]			1
ACR-50 at Week 24			
Responder	4 (3%)	80 (33%)	81 (33%)
Odds ratio vs PBO + MTX [a.]		17	12
95% CI for odds ratio		[3, 118]	[2, 80]
p-value [c.]		0.004	0.011
Odds ratio vs CZP 200 mg + MTX [b.]			1
95% CI for odds ratio			[1, 2]
p-value [c.]			0.9
Treatment by Region Interaction [d.] p-value = 0.50			
ACR-70 at Week 24			
Responder	1 (0%)	39 (16%)	26 (11%)
Odds ratio vs PBO + MTX [a.]		24	15
95% CI for odds ratio		[3, 176]	[2, 115]
p-value [c.]		0.002	0.008
Odds ratio vs CZP 200 mg + MTX [b.]			0.6
95% CI for odds ratio			[0, 1]
p-value [c.]			0.113
Treatment by Region Interaction [d.] p-value = 0.14			

Clear from the second table is the fact that a more typical percentage of subjects treated with this type of product achieved ACR50 and ACR70 responses. The secondary outcome measure of Major Clinical Response, defined as achieving an ACR70 for six consecutive months, also demonstrated a statistically significant treatment effect for the Cimzia arms compared to the placebo arms. The mTSS analysis in Study 027 demonstrated statistically significant treatment effects for both Cimzia arms compared to placebo at a level that has been previously used by the Division to describe highly active agents that may be described as "inhibiting" radiographic progression. Finally, an analysis of the change in Health Assessment Questionnaire – Disability Index (HAQ-DI), an accepted measure of physical function in RA patients, demonstrated a statistically significant treatment effect in the Cimzia treatment arms compared to the placebo arm. The degree of improvement was at a level that clearly exceeded the level that has been shown to represent a clinically meaningful change.

Based on the above results, the clinical and statistical review teams have recommended approval of the dosing regimen that includes the loading dose. Ms. Meaker and Dr. Price have, in particular, recommended not including the results from Study 11, the monotherapy study. They note that, as this dosing regimen is approved for the Crohn's indication but not the RA indication, there could be confusion regarding the appropriate dosing regimen to be used for an individual patient. Dr. Siegel disagrees with this recommendation stating that he believes that it would be important to have the available efficacy data from the monotherapy study in the label because he is recommending that monotherapy be an approved alternative mode of administration since it does provide some degree of effectiveness and may be a more appropriate dosing regimen in some patients. However, he acknowledges that the label would need to clearly describe that the efficacy seen with Cimzia used concomitantly with MTX is greater than with monotherapy. I concur with Dr. Siegel that including the monotherapy efficacy results and dosing regimen would be important and would not be unsafe or misleading.

8. Safety

There are well-documented serious though uncommon adverse effects associated with the TNF-blocking class of therapeutics, including opportunistic infections and reactivation of latent tuberculosis (TB), malignancies, demyelinating disorders and autoimmune diseases. According to the clinical review team, the safety profile of Cimzia appeared to be similar in regard to these potentially serious adverse effects. A total of 2367 RA patients were treated with Cimzia at the doses recommended for marketing. This included 2204 patients treated for three months or longer, 2030 treated for six months or longer, and 1663 treated for twelve months or longer.

The sponsor's safety committee adjudicated the cause of death for the subjects who died during the clinical studies. They determined that there were a greater number of deaths due to cardiovascular events in the Cimzia-treated subjects compared to the placebo-treated subjects. Drs. Yancey and Siegel reviewed the death narratives, readjudicated a number of cases attributed to possible cardiovascular toxicity to be primarily related to infection, and concluded that, although the absolute numbers and the rates of deaths due to cardiovascular causes were higher in Cimzia-treated subjects compared to the placebo-treated subjects, the absolute numbers were small and not likely to represent an increased risk associated with exposure to Cimzia. I would suggest that, even with the numbers as counted by Drs. Yancey and Siegel, there appears to be a possible signal of cardiovascular toxicity related to Cimzia exposure. As such, I reviewed the cases as described by Dr. Yancey in her review and came up with a different conclusion with regard to which deaths were potentially attributable to cardiovascular toxicity. Using my own adjudicated numbers, and including two deaths that had been excluded by the clinical review team for unclear reasons, I concluded that, in the controlled trials, nine of the deaths in the Cimzia treated-subjects were possibly due to cardiac causes and, hence, cardiovascular toxicity, while two were not, and that the single death in a placebo-treated subject was likely to be due to cardiac causes. These numbers calculated out to incidences of 0.5% and 0.2% for the Cimzia-treated vs. the placebo-treated subjects, respectively. Although Dr. Yancey states in her review that there is no signal of cardiac

serious or non-serious adverse events, based on my review of her summary tables, there seems to be an increase in the incidence of these events in the Cimizia arms compared to the placebo arms. Therefore, it appears that there is a potentially concerning signal of cardiovascular toxicity associated with exposure to Cimzia and that further exploration is warranted in order to allow an informed risk-benefit analysis.

Infections were the most common cause of serious adverse events in the Cimzia-treated subjects and occurred nearly four times as frequently in those subjects compared to the placebo-treated subjects. TB developed in 9 subjects exposed to Cimzia and in none of the placebo-treated subjects in the controlled trials. There were 26 cases of TB overall in the RA development program. Of note, none of the cases occurred at North American study sites and the majority occurred at Eastern European sites. As subjects were screened with a PPD skin test and, if positive, treated prior to receiving treatment with Cimzia, Dr. Siegel suggests that these results indicate that standard procedures for preventing reactivation of TB may not be adequate in highly endemic areas. Another possibility is that, (as noted in Dr. Yancey's review), patients in BCG-vaccinated areas which include France and Eastern Europe may have had a different risk profile due to the difficulty of distinguishing post-PPD test induration due to previous vaccination from induration due to previous TB infection. Other infections resulting in serious adverse events included lower respiratory infections, bacterial infections and upper respiratory infections. The overall rate of infections was also higher in the Cimzia-treated subjects compared to the placebo-treated subjects.

In regard to malignancies, Dr. Yancey states, on page 185 of her review, that "In summary, these data suggest that there does not appear to be increased risk of developing a malignancy in patients treated with CZP [*Cimzia*]." However, on the same page she reviews the number of observed cases of malignancy in the clinical study database compared to the GLOBOCAN and SEER databases (representing background rates in the community) and notes that, while there was not an increased number of observed cases of malignancy overall, there was a three-fold increase in the number of observed cases of lymphoma compared to the expected numbers from these databases, i.e., 3 observed vs. 0.6 and 0.97 for the GLOBOCAN AND SEER, respectively. However, as Dr. Siegel notes on page 23 of his review, the rate of lymphoma is known to be increased in RA patients and the standardized incidence ratio of 5 (calculated by dividing the number of observed cases, 3, by the number of expected cases from the GLOBOCAN, 0.6) is within the range previously observed in RA patients receiving TNF blockers. Therefore, it would be more accurate to state that there is an increased risk of developing a malignancy, and particularly lymphoma, associated with exposure to Cimzia; however, that risk is approximately the same as the risk seen with the three approved TNF blocking agents.

Antibodies to certolizumab did develop in some patients. The following table, reproduced from page 24 of Dr. Siegel's review, summarizes the data regarding antibody development in the clinical studies:

Table 5: Anti-CZP Antibody Positive Patients in CZP RA Studies

Anti-CZP Antibody Positive Patients - Study 011, 014, 027 and 050 in RA					
	CZP 200 mg [(a.)] sc q2w + MTX N = 640	CZP 400 mg sc q2w + MTX N = 633	CZP 400 mg sc q4w + MTX N = 124	CZP 400 mg sc N = 111	All CZP Doses N = 1508
Antibody Positive	63 (10%)	12 (2%)	5 (4%)	25 (22.5%)	105 (7%)

Efficacy was diminished in the patients who developed anti-certolzumab antibodies. Some patients treated with Cimzia also developed autoantibodies (anti-dsDNA and ANA) and some patients developed a lupus-like syndrome. The clinical review team notes that these findings have also been seen with the approved TNF blocking agents.

9. Advisory Committee Meeting

The Division concluded that it was not necessary to take this application to an Advisory Committee meeting for discussion as this is the fourth TNF-α blocking agent developed to treat RA and there were no special safety concerns noted for Cimzia upon initial review of the application for filing. However, should further exploration of the possible cardiovascular toxicity signal not completely exonerate Cimzia of this risk, the sponsor's response to a CR action will likely need to be presented to the Arthritis Advisory Committee.

10. Pediatrics

The clinical review team has determined that it is acceptable to extrapolate the efficacy demonstrated in adults to pediatric patients with polyarticular JIA. Therefore, no efficacy study will be required. However, under PREA the sponsor will need to study the safety, immunogenicity and pharmacokinetics of Cimzia in children. With the concurrence of the Pediatric Review Committee, upon approval, the sponsor will be granted a deferral of studies in the 2 to 17 years of age group and a waiver for the 0 to 2 years of age group, based on the prevalence of polyarticular JIA.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The review team proposed a number of labeling changes to the package insert which have been agreed upon by the sponsor. However, as we are unable to approve the drug at this time, we will need to reassess the label language on the next review cycle.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Complete Response

- Risk Benefit Assessment

The sponsor has provided adequate evidence to support the efficacy of Cimzia for the treatment of RA. However, although the clinical review team has concluded that there is not a cardiovascular safety concern for Cimzia, I remain unconvinced of this after reviewing the data myself and after extensive discussion with the team. Therefore, I must err on the conservative side and assume that this is a real signal until adequate evidence has been provided to allay my concern. The cardiovascular safety signal seen in the RA safety database was apparently not seen in the Crohn's disease database. This could reflect the increased risk for cardiovascular disease that RA patients have as a baseline; or the apparent imbalance in cardiovascular adverse events, including deaths, in the Cimzia-treated subjects could be due to spurious data or simply be a reflection of the study design, e.g., the unequal randomization and resultant small number of placebo-treated subjects. In any case, this signal will require further exploration either by reanalysis of the available data or by performing an additional study or studies. As it stands, I am unable to make a reasonable assessment of the risk-benefit ratio for Cimzia based on the data and analyses that are currently available.

In regard to the monotherapy efficacy data and dosing regimen, both the statistical and the clinical pharmacology review teams recommended exclusion of this information from the label as the monotherapy study did not include the loading dose which clearly improved the product's effectiveness. Dr. Siegel and I differed with this recommendation due to the importance of providing information on the documented efficacy of Cimzia as monotherapy and offering this dosing regimen as an approved alternative to combination therapy. We reached this conclusion because, in spite of the fact that combination therapy with MTX clearly offers an increased level of effectiveness over monotherapy, there are some patients for whom monotherapy may be the more appropriate treatment regimen due to safety or tolerability concerns in regard to MTX. Additional discussion was undertaken and the statistical and clinical pharmacology review teams were satisfied that our reasoning made sense from a clinical perspective and they concurred with the labeling language that we have proposed.

- Recommendation for Postmarketing Risk Management Activities

This application has an approved REMS (Medication Guide) under BLA 125160. Because this application will become a supplement immediately following action, it

will not have a separate REMS from the currently approved on under BLA 125160. On September 4, 2008, the Agency sent a supplement request letter to the Sponsor requesting a modification to the REMS. This modification included changes to the Medication Guide to incorporate new safety data regarding histoplasmosis and to create a Communication Plan. This labeling change was approved on December 22, 2008, and Communication Plan was approved on December 31, 2008, under BLA 125160.

- Recommendation for Postmarketing Study Requirements

The only postmarketing study requirements will be the pediatric studies discussed in Section 10 above, required under PREA.

- Recommendation for Postmarketing Study Commitments

Dr. Rellahan recommended two postmarketing study commitments, which were agreed to by the Sponsor on December 24, 2008.

1. Re-evaluate the drug product sub-visible release and shelf-life specifications upon confirming the feasibility of a preparatory method that will enable implementation of the USP <788> preferred method. The data and specification assessment will be provided within two years from the time of approval.

Study Completion:	January 2011
Final Report Submission:	April 2011

2. Provide a commitment to conduct additional studies to evaluate the process-specific assay test for the assessment of HCP per your July 31, 2008 submission. A summary report and data will be provided by January 31, 2009.

Study Completion:	January 2009
Final Report Submission:	February 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Memo

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation 2
Division of Anesthesia, Analgesia and Rheumatology Products

Cross-Discipline Team Leader Memorandum

Date: May 4, 2009

To: File, BLA 125271/0

From: Jeffrey Siegel, M.D. Jeffrey N. Siegel 5/4/09
Clinical Team Leader
ODE2 - Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Re: Need for additional studies of blood pressure effects of Cimzia
CIMZIA® (certolizumab pegol)
UCB, Inc.
Proposed indication: Rheumatoid arthritis

This memo addresses an issue raised in the April 29, 2009 consultation from the Cardiorenal Division concerning the complete response from the Applicant, UCB. The previous consultation from the Cardiorenal Division had raised concerns about five issues concerning the risk of cardiovascular adverse events with Cimzia: heart failure/cardiomyopathy, tachyarrhythmia/tachycardia, stroke/transient ischemic attacks, hypertension and venous thrombosis/phlebitis. The review of the Applicant's response from Cardiorenal concluded that the Applicant's responses for four of the five issues were acceptable. For the fifth issue, hypertension, the Cardiorenal Division had concerns that the new data submitted by the Applicant weren't not fully satisfactory for addressing the issue. They said that the most helpful additional information would be a careful study of BP changes throughout the interdosing interval and with long term follow-up. They further stated that whether and when to require such a study was the decision of DAARP.

The basis for the concern regarding hypertension derives from an analysis conducted by Cardiorenal showing a higher rate of hypertensive adverse events with Cimzia (5.4%) than placebo (1.6%). When adjusted for a longer duration of exposure for Cimzia-treated patients than controls there was still a higher rate of hypertensive AE's. Blood pressure measurements at the end of the dosing interval did not show mean blood pressure to be higher in Cimzia-treated patients than controls. However, this left open the possibility that blood pressure might be elevated earlier in the dosing interval. The Applicant submitted several analyses to further address the issue. The data show that hypertensive AE's were more frequent in patients with a baseline history of hypertension than in those without; that the incidence of blood pressure measurements exceeding 140/90 in the postdosing period was not higher in the Cimzia group than controls; that the hypertensive AE's were not more frequent in the post-dose period than in other periods; that most of the hypertensive AE's were mild or moderate in severity; and that hypertensive AE's were more common among patients receiving concomitant non-steroidal anti-inflammatory drugs (NSAID's) or corticosteroids.

In summary, there was a higher incidence of hypertensive AE's in patients receiving Cimzia than in controls. Although data are not comprehensive, analysis of direct measurement of blood pressure did not show an effect of Cimzia on blood pressure in the postdose or the predose period. Given that this patient population is at risk for hypertension and that hypertensive AE's occurred in patients at risk these AE's were not unexpected. The risk of developing hypertension should be clearly described in the Cimzia label but based on the available data further study of hypertension in patients receiving Cimzia is not necessary.

Cross-Discipline Team Leader Memo

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation 2
Division of Anesthesia, Analgesia and Rheumatology Products

Cross-Discipline Team Leader Memorandum

Date: December 18, 2008

To: File, BLA 125271/0

From: Jeffrey Siegel, M.D. Jeffrey M. Siegel 12/18/08
Clinical Team Leader
ODE2 - Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Re: BLA 125271/0
CIMZIA® (certolizumab pegol)
UCB, Inc.
Proposed indication: Rheumatoid arthritis

TABLE OF CONTENTS

1. Introduction to Review

UCB submitted this biologic licensing application (BLA) seeking the approval of certolizumab pegol (CZP) for the treatment of patients with rheumatoid arthritis (RA). CZP is a PEGylated monoclonal antibody Fab' fragment that binds to tumor necrosis factor-α (TNF), thereby inhibiting its biologic activity. CZP is currently approved for the treatment of Crohn's disease. The Applicant submitted data from four Phase 3 trials of CZP in RA. Two trials used the dosing regimen recommended for approval in combination with methotrexate (MTX) and included every 2 week dosing and an initial loading dose. The other two trials were conducted earlier and used every 4 week dosing and no initial loading dose: one investigated CZP monotherapy; the other combination therapy with MTX. Overall, the safety database in the RA clinical development program consisted of a total of 2367 patients treated with CZP at the doses recommended for marketing, including 2204 treated for 3 months or longer, 2030 treated for 6 months or longer and 1663 treated for 12 months or longer. The Applicant proposes administration of CZP subcutaneously beginning with a loading dose of 400 mg every 2 weeks for 3 doses followed by 200 mg every 2 weeks.

During the review of this application, important issues arose regarding product quality, clinical pharmacology, clinical efficacy and clinical safety, OSE review of the proposed packaging, what studies should be required under PREA and the need for a postmarketing registry. The product quality issues involve assurance that the levels of the genotoxic compound (b) (4) in the product are adequately low. The Clinical Pharmacology and clinical efficacy issue concerns immunogenicity of the product when given as monotherapy and efficacy of every 4 week dosing. The clinical safety issue involved an apparent excess of cardiovascular deaths in the certolizumab pegol arms of the randomized trials in the Applicant's submission. The OSE concern related to the potential for confusion if the new prefilled syringe formulation and the older lyophilized formulations are both marketed at the same time. The issue concerning PREA was whether an efficacy trial should be required in children with juvenile idiopathic arthritis (JIA). The issue concerning a postmarketing registry is whether the Applicant should be required to conduct a registry to assess safety of certolizumab given that it is the fourth product in this class for RA. At the time of this review most of these issues have been adequately addressed. The issue concerning (b) (4) is in the process of being addressed as are the issues concerning requirements under PREA and the need for a postmarketing registry. This memo will review the regulatory background for this application, the evidence supporting efficacy and safety of tocilizumab in RA and key findings in other disciplines.

2. Background – Regulatory history

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory condition that primarily affects the joints but can also affect other organs. Active RA is associated with pain and physical impairment. If left untreated or inadequately treated RA leads to progressive damage to joints with subsequent disability and the need for joint replacement. The FDA Guidance for Industry on clinical development programs for RA

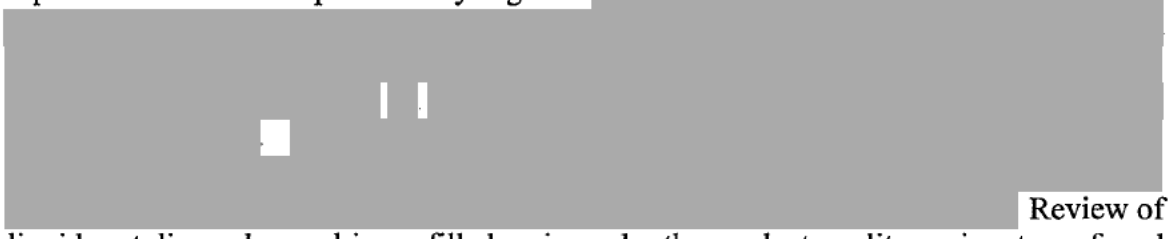
(RA guidance document) describes the types of clinical trials needed for approval of products for RA. The basic claim usually assessed in clinical trials for approval is improvement in signs and symptoms as measured by an accepted composite index such as the ACR 20 (American College of Rheumatology 20). Claims describing additional benefits that can be assessed in clinical trials include improvement in physical function, major clinical response, inhibition of progression of structural damage, complete clinical response and remission. In addition to the basic claim of treatment of signs and symptoms of RA, the Applicant is seeking claims of improvement in physical function, major clinical response and inhibition of progression of structural damage.

The drug development program for certolizumab in RA began with a Phase 2, dose-finding trial followed by two Phase 3 trials (Studies 011 and 014). Those studies met their primary efficacy endpoint of ACR 20 response at 6 months; however, the Applicant noted that the indicators of more substantial clinical response, ACR 50 and 70, were lower than has been observed with other TNF blockers and the ACR 20 responses were somewhat lower as well. Therefore, the Applicant met with the Agency in October, 2004, to discuss plans for conducting two additional Phase 3 trials to explore an alternative dosing regimen that added an initial load and more frequent, every other week, dosing. After completion of those additional Phase 3 studies (Studies 027 and 050) the Applicant submitted a biologic licensing application (BLA) for certolizumab pegol (Cimzia) for the treatment of rheumatoid arthritis. At the same time the Applicant had submitted a BLA for approval of certolizumab pegol for treatment of Crohn's disease. That BLA was approved in April, 2008.

3. CMC/Microbiology/Device

3.1. General product quality considerations

Certolizumab pegol is already approved and marketed as a lyophilized powder. For the current submission the Applicant submitted data to support their proposal to market a liquid formulation in prefilled syringes. (b) (4)



Review of liquid certolizumab pegol in prefilled syringes by the product quality review team found no issues that would prevent the approval of this new dosage form.

The Division of Monoclonal Antibodies review team stated that all issues were resolved during the review in a satisfactory manner with the exception of two unresolved issues, which they determined could be addressed as CMC post-marketing commitments. The two issues involved a re-evaluation of drug product sub-visible particulates release and shelf-life specifications and the evaluation of the process-specific assay test for the assessment of host cell protein (HCP).

The Pharmacology/toxicology review team raised concerns about the possibility of (b) (4) in certolizumab. This issue will be addressed further under section 4. In addition, DMEP raised concerns about safety issues that may arise if UCB markets both a lyophilized product and a prefilled syringe. These issues will be discussed further under section 6.3.6.

3.2. Facilities review/inspection

The facilities inspection identified some deficiencies; however, the final review is not available at the time of writing of this memorandum. Patricia Hughes related to me verbally on December 9, 2008 that review of those deficiencies determined that no official action was required and that the application could be approved from the point of view of Compliance. She said she would write an official memorandum to that effect.

4. Nonclinical Pharmacology/Toxicology

Review of the pharmacology/toxicology section of the application revealed no issues that would prevent approval. The reviewer noted that Cimzia was approved in April, 2008 by the Division of Gastroenterology Products. However, the pharmacology/toxicology reviewer expressed concern about the lack of information about the levels of (b) (4) present in the drug product and drug substance. (b) (4) a toxic substance that is also genotoxic and is a reproductive toxin. The review team recommends a post-marketing commitment to determine levels of (b) (4) in drug substance and drug product. Depending on the information provided there may be a need for measuring (b) (4) levels in humans, further risk assessment and for setting specification levels. I concur with their assessment.

5. Clinical Pharmacology/Biopharmaceutics

5.1. General clinical pharmacology/biopharmaceutics considerations

The PK of certolizumab was similar in healthy volunteers and RA patients. Mean clearance values were 0.13 - 0.20 ml/hr/kg with a mean terminal phase half-live of 13 – 15 days. The volume of distribution was similar to total blood volume (60 – 102 ml/kg). Bioavailability of subcutaneously administered certolizumab was approximately 80%.

Some patients receiving certolizumab pegol developed anti-product antibodies. Patients who developed anti-certolizumab antibodies had lower blood levels of certolizumab due to increased clearance and were less likely to have a clinical response. The likelihood of developing anti-certolizumab antibodies was increased in patients who received certolizumab monotherapy compared to patients receiving certolizumab in combination with methotrexate (MTX).

Exposure-response modeling indicated that optimal ACR 20 responses were associated with trough certolizumab levels of 10 mcg/mL. The proposed load allows steady state levels to be achieved more quickly. The mean trough level for patients receiving the

proposed dose regimen exceeded the threshold of 10 mcg/mL; however, more patients achieved trough levels of 10 mcg/mL in the 400 mg q2wk arm than in the 200 mg q2wk arm. The proposed alternative dose regimen of 400 mg q4wk is associated with lower trough levels with exposure-response modeling, suggesting that the likelihood of achieving an ACR20 response is reduced from 70% to 50% with the q4w regimen as compared to the q2wk regimen. Based on the expectation of lower trough levels and predicted lower ACR20 responses with the q4wk regimen, and further lowering of certolizumab levels with monotherapy due to greater immunogenicity, the Clinical Pharmacology review team believes that the alternative 400 mg q4wk regimen is inappropriate for patients not receiving concomitant MTX. For labeling the review team suggests that the 400 q4wk regimen be recommended only for patients receiving concomitant MTX.

Population PK analysis evaluated the effect of age, body weight, race, gender, anti-certolizumab antibody status, concomitant medications (methotrexate, glucocorticoids, NSAIDs, other DMARDs) and laboratory assay on the PK of certolizumab. The analysis identified body weight and antibody status as important covariates influencing clearance, with antibody status being the major contributor to variability in clearance. Despite the influence of body weight on the PK of certolizumab, the Clinical Pharmacology review team concluded that fixed dosing is appropriate since the probability of ACR20 response is similar (~70%) across all body weight quartiles due to the shallow body weight – C_{trough} relationship and high enough exposures at the proposed dosing regimen

5.2. Drug-drug interactions

Since immunoglobulin molecules are not metabolized by P450 enzymes, direct pharmacokinetic interaction via the CYP pathway is not expected between certolizumab and small molecules. Hence, formal drug-drug interaction studies were not conducted and they were not considered necessary. Studies of MTX pharmacokinetics were carried out in patients receiving certolizumab pegol and showed no significant effect on MTX pharmacokinetics. As described above, MTX coadministration did have an important effect on certolizumab blood levels by reducing the likelihood of developing anti-certolizumab antibodies.

5.3. Pathway of Elimination

For antibodies such as certolizumab, two types of pathways mediate elimination mechanisms: a nonspecific linear clearance by the reticuloendothelial system and an antigen-mediated saturable clearance.

5.4. Demographic interactions/special populations

Population PK studies that evaluated the effect of age, race and gender found no significant interactions. No information was submitted on PK in children. The Applicant has requested a deferral for pediatric studies.

5.5. Thorough QT study or other QT assessment

The effects of certolizumab on QT were not formally assessed as biologic products like certolizumab are generally not expected to interact with cardiac ion channels.

5.6. Notable issues

For labeling the Clinical Pharmacology review team suggests that the alternative certolizumab 400 mg q4wk dose regimen be recommended only when certolizumab is administered in combination with MTX and not with certolizumab monotherapy. They also recommend a post-marketing study of PK/PD in children with juvenile idiopathic arthritis. Regarding the alternative 400 mg q4wk dose regimen, while it is true that efficacy for this regimen given as monotherapy is less than when it is given in combination with MTX, that regimen was tested and demonstrated to be efficacious (see Section 6, Clinical/Statistical below). Clinically, while TNF blockers are generally prescribed in combination with MTX, MTX does have serious toxicities associated with its use, including pulmonary toxicity, hematologic toxicity and liver toxicity so it would be important to offer to clinicians proven efficacious options for certolizumab use in patients who do not wish to take MTX or who cannot tolerate it. Rather than not offering the 400 mg q4wk regimen as an option for certolizumab monotherapy I would favor clearly communicating the increased risk of anti-certolizumab antibody formation and the lower level of efficacy shown with this alternative regimen.

Regarding the recommendation that PK/PD studies be conducted in children post-marketing, I am in agreement.

6. Clinical/Statistical

6.1. General Discussion

The Applicant submitted results of four Phase 3 trials of efficacy and safety in patients with RA. In general, the Applicant followed advice provided by the Agency in the End of Phase 2 meeting on the design and analysis of the clinical trials and on acquiring adequate data to assess safety. All patients had established disease and most had an incomplete response to MTX. The Applicant submitted data to support a signs & symptoms claim as well as claims of inhibition of progression of structural damage, improvement in physical function and major clinical response. Significant issues regarding efficacy include whether the efficacy is adequate with monotherapy and with 400 mg q4w dosing to recommend these dose regimens. Significant safety issues include a higher rate of serious infections with certolizumab, including a large number of cases of tuberculosis despite screening and treatment for latent tuberculosis infection in patients who screened positive. An increased risk of infection, including tuberculosis, is an expected event for certolizumab based on its immunosuppressive mechanism of action and on prior experience with other products in this class.

6.2. Efficacy

6.2.1. Dose identification/selection and limitations

The Applicant conducted an initial dose-finding study in which patients received placebo or study drug SC every 4 weeks x3 at doses of 0 (placebo), 50, 100, 200, 400, 600 or 800. ACR20 responses at week 12 were 15%, 21%, 20%, 34%, 60%, 64%, and 79%, respectively. Based on these findings the Applicant carried out their two initial Phase 3 studies using a dose of 400 mg SC q4wks. Study 011 was a randomized, placebo-controlled trial of certolizumab monotherapy in patients with active RA. The analysis population was a modified intent-to-treat population that included all randomized patients who received at least one dose of study drug. Study 014 had a similar design but studied certolizumab treatment as add-on to background stable doses of MTX. As shown in Table 1 (this and all other tables and figures copied from the clinical review by Dr. Carolyn Yancey), treatment with certolizumab 400 mg SC q4wk was associated with an increase in the proportion of patients achieving the primary endpoint, the ACR20. However, relatively few patients achieved the higher level ACR 70 response (Table 2, statistical testing utilized the Cochran-Mantel-Haenszel test). In contrast to the 6% of certolizumab-treated patients achieving an ACR 70 response in Study 011 the proportion of patients achieving similar levels of response in studies of other TNF blockers has been in the mid-teens. Similarly, in Study 014 of certolizumab in combination with MTX ACR20 responses were observed (Table 3) but no ACR 70 responses (Table 4). In contrast, later, in studies using a loading dose of 400 mg SC q2wk x3 followed by 200 mg or 400 mg SC q2wk ACR 50 response rates of 33-40% and ACR 70 response rates of 11-21% were seen at Week 24 (see below, Studies 027 and 050).

Table 1: ACR20 Response at Week 24 – Study 011

ACR20 Response at Week 24 - Primary Analysis - Study 011 (mITT Population)			
	PBO N = 109	CZP 400 mg sc q4w N = 111	p-Value [a.]
Responder [b.]	10 (9%)	50 (46%)	<0.001

(a.) Cochran-Mantel-Haenszel (CMH) test of treatment comparison stratified by country.
(b.) A patient was considered a responder if he/she met the criteria of ACR20 improvement over Baseline at Week 24. Any patient who withdraws from the study at any time for any reason was considered a non-responder. Revised from sponsor Table 14.2.1:1, page 428 of 5470.

Table 2: ACR70 Response at Week 24 – Study 011

ACR70 Response at Week 24 - Study 011 (mITT population)			
Week 24	PBO N = 109	CZP 400 mg q4w N = 111	p-value
Responder [a.]	0	6 (6%)	0.013

Table 3: Primary Endpoint Analysis and Sensitivity Analyses, ACR20 Response – Study 014

ACR20 Response at Week 24 - Study 014			
Sensitivity Analysis (mITT)			
	PBO + MTX N = 119	CZP 400 mg sc q4w + MTX N = 124	p-Value [a.]
Responder [b.]	32 (27%)	59 (48%)	<0.001
Sensitvity Analysis - Excuding Protocol Violators (mITT)			
Responder [b.]	21 (27%)	45 (50%)	0.002
Sensivity Analysis - Excluding CZP Treated Protocol Violators (mITT)			
Responder [b.]	27 (23%)	45 (50%)	<0.001
(a.) Cochran-Mantel-Haenszel (CMH) test of treatment comparison stratified by country. (b.) A patient was considered a responder if he/she met the criteria for ACR20 improvement over Baseline at Week 24. Any patient who withdrew was considered a non-responder. Abbreviations: PBO=placebo; MTX=methotrexate; mITT= modified intent-to-treat. Revised from sponsor Table 14.2.1:2, page 443 of 6006.			

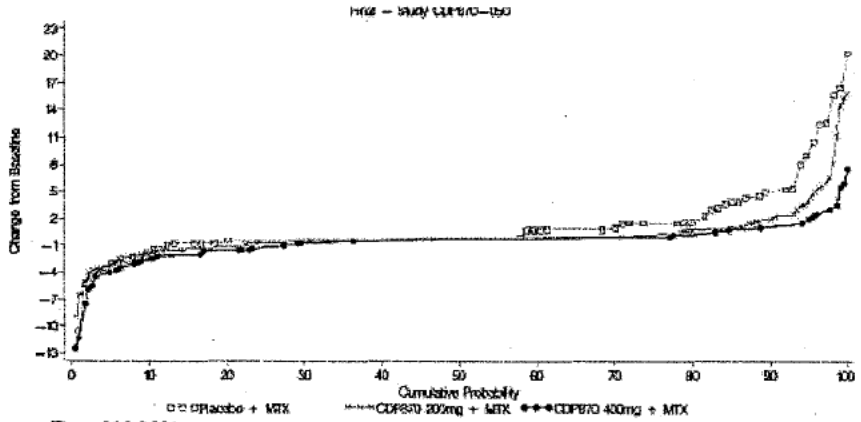
Table 4: ACR50 and ACR70 at Week 24 – Study 014

ACR50 and ACR70 at Week 24 - Study 014 (mITT)			
	PBO + MTX (N=119)	CZP 400 mg q4w + MTX (N=124)	p-value [a.]
ACR-50			
Week 24, Responder	7 (6%)	22 (18%)	0.004
ACR-70			
Week 24, Responder	2 (2%)	0	0.133

While the results from Studies 011 and 014 suggest that certolizumab 400 mg SC q4wk is efficacious, it also appears to be a suboptimal dose. After completing Studies 011 and 014, the Applicant made two changes to the dose regimen for certolizumab for the subsequent studies. They added an initial load consisting of 400 mg SC q2wk x3 and changed the dosing interval to q2wks for maintenance dosing. As will be described in more detail in section 6.2.2 these later studies (027 and 050) showed efficacy of certolizumab 200 mg q2wks and 400 mg q2wks and achieved response rates similar to what has been seen with other TNF blockers.

Detailed examination of the results of Studies 027 and 050 suggest that overall the efficacy of the 200 mg and 400 mg SC q2wk doses are similar. However, there are a few findings indicating that the 400 mg dose may be slightly better. Although the ACR response rates were similar for the 200 mg and 400 mg SC q2wk doses, the 200 mg dose was more immunogenic. In Study 027, 11% of patients receiving certolizumab 200 mg became anti-certolizumab antibody positive compared to 2% of patients receiving certolizumab 400 mg. Similarly, in Study 050 8.5% of patients receiving certolizumab 200 mg became anti-certolizumab antibody positive compared to 1.6% of patients receiving the 400 mg dose. Also, while radiographic progression was inhibited in both studies as measured by the change from baseline in modified total Sharp score (mTSS) the degree of inhibition was somewhat greater with the 400 mg dose in Study 050. This modest difference between doses can be seen in the cumulative probability plot for radiographic progression (Figure 1). In this analysis changes from baseline in mTSS are

shown on the y-axis and the cumulative percentage of patients with a particular level of change in mTSS is shown on the x-axis. Higher values of change in mTSS represent greater levels of radiographic progression. As shown in Figure 1 the curves for placebo, 200 mg and 400 mg are similar on the left side of the graph representing patients with little or no radiographic progression. In contrast, the proportion of patients with moderate or large amounts of radiographic progression is markedly lower with certolizumab 400 mg than with placebo as shown on the right side of the figure. The middle curve representing the 200 mg dose is reduced compared to placebo but not quite as much as the 400 mg dose. In contrast, the cumulative probability curve of radiographic progression showed similar inhibition with the 200 mg as with the 400 mg dose in Study 027.



Source: Figure 14.2.5:104

Figure 1: Cumulative Probability Plot of the Change from Baseline in mTSS at Week 24 – Linear Extrapolation – Study 050 (ITT Population) [Sponsor Figure 11:8) page 112 of 6142.]

In summary, there are some differences between the 200 and 400 mg doses that would favor the higher dose, most importantly a somewhat lower level of immunogenicity with the 400 mg dose. Nonetheless overall ACR response rates are similar between the two doses and both doses achieve substantial levels of inhibition of progression of structural damage. In general, the differences between the 200 and 400 mg doses are not large enough to favor the higher dose over the lower one given the potential for more safety concerns with higher doses than with lower doses. Taken in their entirety the data suggest that 200 mg q2wk is an appropriate recommended dose.

The proposed dose regimen also contains an initial loading dose of 400 mg SC q2wk x3. The use of this loading dose is supported by the PK modeling that suggests a shorter time to achieving therapeutic blood levels. The better overall results in Studies 027 and 050, which used the loading dose, as compared to 011 and 014, which did not, supports the importance of the loading dose. However, Studies 027 and 050 also differ from the earlier studies in incorporating more frequent q2wk as compared to q4wk dosing.

Finally, the Applicant is proposing an alternative dosing regimen of 400 mg q4wks and proposes that certolizumab may be used as monotherapy or in combination with MTX. As described above, Studies 011 and 014 demonstrated the efficacy of 400 mg q4wk dosing and Study 011 demonstrates efficacy of certolizumab monotherapy. While acknowledging that combination with MTX and q2wk dosing may produce higher efficacy the use of certolizumab as monotherapy and of the alternative 400 mg q4wk dosing regimens appear adequately supported by the data.

6.2.2. Phase 3/ clinical studies essential to regulatory decision

The key studies supporting the efficacy of certolizumab are the Phase 3 trials 027 and 050. Both studies were randomized, double-blind, placebo-controlled, 3-arm trials in patients with active RA despite MTX. Patients in the two certolizumab arms received a loading dose of certolizumab at a dose of 400 mg SC q2wk x3 followed by either 200 mg q2wk or 400 mg q2wk. Both trials contained a primary endpoint of the proportion of patients achieving an ACR20 at 6 months. Study 027 additionally included a second coprimary endpoint assessing radiographic progression using the change from baseline in modified total Sharp score (mTSS). The protocol specified a sequential approach to control for multiplicity by examining the mTSS only if the study had already found statistical significance for the ACR20 coprimary endpoint. The analysis population was the intent-to-treat population, i.e., all randomized subjects.

In general, the populations in Studies 027 and 050 were typical of the general RA population. The mean age was approximately 50 years and the mean duration of disease was 6 years. Approximately 80% were female. Patients had moderately to severely active RA with mean tender joint counts of approximately 30 and mean swollen joint counts of approximately 20.

The studies permitted patients to discontinue study mediation early for patients who failed to respond by week 16. Approximately 90% of patients had adequate information to assess the primary endpoint either based on the ACR20 status at 6 months (completers) or based on demonstrated lack of efficacy at week 16 or later (Table 5 from Study 027, similar results were seen in Study 050). Patients with missing data were imputed as non-responders. Discontinuations were more frequent for lack of efficacy in the placebo arms than in the certolizumab arms. Discontinuations due to adverse events were more frequent in the certolizumab arms than in the placebo arms.

Table 5: Patient Disposition: Withdrawals (ITT) – Study 027

Patient Disposition - Study 027 (ITT Population)				
	PBO + MTX	CZP 200 mg q2w+MTX	CZP 400 q2w+MTX	Overall
All patients				1262 (100%)
Screening failures				280 (22%)
Randomized (ITT)	N = 199	N = 393	N = 390	N = 982 (100%)
Safety population	199 (100%)	392 (99.7%)	389 (99.7%)	980 (99.8%) [a]
PP (signs, symptoms)	192 (96%)	370 (94%)	378 (97%)	940 (96%)
PP (structural damage)	191 (96%)	371 (94%)	377 (97%)	939 (96%)
Withdrawn at Week 16	125 (63%)	83 (21%)	68 (17%)	276 (28%)
Completed at Week 16	173 (87%)	355 (90%)	357 (92%)	885 (90%)
Completed at Week 24	45 (23%)	264 (67%)	288 (74%)	597 (61%)
Completed at Week 52	43 (22%)	255 (65%)	274 (70%)	572 (58%)
Total Discontinuations	156 [c] (78%)	138 [c] (35%)	116 [c] (30%)	410 [c] (42%)
Lack of efficacy	141 (71%)	98 (25%)	74 (19%)	313 (32%)
Discontinued due to AEs	3 (2%)	17 (4%)	22 (6%)	42 (4%)
Protocol violations	0	4 (1%)	3 (0.8%)	7 (0.7%)
Patient decision, consent w/dr.	10 (5%)	15 (4%)	11 (3%)	36 (4%)
Lost to follow-up / Unknown	1 (0.5%)	1 (0.3%)	1 (0.3%)	3 (0.3%)
Other [b]	3 (2%)	5 (1%)	6 (2%)	14 (1.4%)
Pts. with non-missing data for the primary efficacy endpoint [d]	93%	90%	89%	90%

(a.) Two patients were randomized but did not receive study drug: Pt.# 118/004 randomized to 200 q2w+MTX withdrew her consent; Pt. #135/005 randomized to 400 q2w+MTX was discontinued due to abnormal ESR/CRP not meeting entry criteria.

(b.) One death (Pt. # 052/002) is reported in the PBO-control treatment group and one death (Pt. # 068/014) is reported in the 400 mg q2w + MTX treatment group. See safety review section for total number of deaths in Study CDP870-027.

(c.) Total discontinuations differ from table #: PBO-Control, 158 vs 156; 200 q2w+MTX, 140 vs 138 ; 400 q2w+MTX, 117 versus 116; Overall 410 vs 415. Abbreviations: PP = per protocol; AEs = adverse events; w/dr.=withdrawn.

(d.) Patients with adequate data who completed or dropped out due to lack of efficacy. Therefore, data is adequate to calculate the primary efficacy analysis for ACR20 responders at Week 52.

Revised from sponsor Table 14.1.1:2,page 261 of 8823.

Certolizumab treatment demonstrated efficacy for signs and symptoms in Study 027 as shown by an increase in the proportion of patient achieving an ACR20 response at 24 weeks, the primary endpoint for the study (Table 6). A total of 59% and 61% of patients achieved an ACR20 response with the 200 mg and 400 mg doses, respectively, vs. 14% with placebo. Similar results were seen in Study 050 (Table 7). More patients achieved the higher levels of clinical response ACR 50 and ACR 70. The findings on the primary endpoint, the ACR20, were verified by the FDA biostatistical reviewer, Dr. Kate Meaker. Dr. Meaker also confirmed that the statistical analytic plan adequately accounted for multiplicity in view of the two doses tested and the two coprimary endpoints. Sensitivity analyses showed similar results indicating that the positive results were not accounted for by missing data.

The results of secondary endpoints supported the efficacy demonstrated by the primary endpoint. The components of the ACR response criteria all showed improvement with certolizumab, indicating the results on the composite was not driven by one or a subset of the seven individual components. More patients achieved a Major Clinical Response in the certolizumab arms than with placebo as defined by an ACR 70 for 6 consecutive months (13% for the two certolizumab arms vs. 1% for placebo). Examination of subgroup analyses based on baseline demographic features and baseline disease activity revealed no subgroup of patients who did not have a response to certolizumab.

Table 6: Co-Primary ACR20 Response at Week 24 and Week 52 – Study 027

ACR Response - Study 027 (ITT Population)			
	PBO+ MTX N = 199	CZP 200 sc q2w + MTX N = 383	CZP 400 sc q2w + MTX N = 390
ACR-20			
Week 24			
n [c.]	198	388	388
Responder	27 (14%)	288 (59%)	236 (61%)
Odds ratio vs PBP+MTX [a.] (97.5% CI)		9 (5, 16)	10 (6, 17)
p-value		<0.001	<0.001
Week 52			
n [c.]	198	392	388
Responder	26 (13%)	208 (53%)	213 (55%)
Odds ratio vs PBO+MTX (95% CI) [b.]		8 (5, 12)	8 (5, 13)
ACR-50			
Week 24			
Responder	15 (8%)	144 (37%)	155 (40%)
Odds ratio vs PBO+MTX (95%CI) [b.]		8 (4, 13)	9 (5, 15)
p-value		<0.001	<0.001
Week 52			
Responder	15 (8%)	149 (38%)	155 (40%)
Odds ratio vs PBO+MTX (95%CI) [b.]		8 (4, 14)	8 (5, 5)
ACR-70			
Week 24			
Responder	6 (3%)	83 (21%)	80 (21%)
Odds ratio vs PBO+MTX (95%CI) [b.]		9 (3, 22)	8.7 (4, 21)
p-value		<0.001	<0.001
Week 52			
Responder	7 (4%)	83 (21%)	90 (23%)
Odds ratio vs PBO+MTX (95%CI) [b.]		8 (3, 17)	9 (4, 9)
p-value		<0.001	<0.001

Abbreviations: MTX=methotrexate; CI=confidence interval; PBO=placebo.
(a.) Odds ratio: CZP/PBO calculated using logistic regression with factors for treatment and region.
(b.) Wald p-values for the comparison of the treatment groups were calculated using logistic regression with factors for treatment and region.
(c.) n remains the same for calculation of the ACR-50 responses at Week 24 and Week 52, respectively.
Note: patients who withdrew or used rescue medication were considered as non-responders from that time-point forward. Revised from sponsor Table 11:11, page 105 of 8823.

Table 7: ACR-20, -50 and -70 Responses – Study 050

ACR Response - Study 050 (ITT Population) - Study 050			
	PBO + MTX	CZP 200 mg sc q2w + MTX	CZP 400 mg sc q2w + MTX
	N = 127	N = 246	N = 246
ACR-20 at Week 24			
n	127	246	245
Responder	11 (9%)	141 (57%)	141 (58%)
Odds ratio vs PBO + MTX [a.]		14	14
97.5% CI for odds ratio		[7, 31]	[7, 31]
p-value [c.]		<0.001	<0.001
Odds ratio vs CZP 200 mg q2w + MTX [b.]			1
95% CI for odds ratio			[1, 1]
p-value [c.]			1
ACR-50 at Week 24			
Responder	4 (3%)	80 (33%)	81 (33%)
Odds ratio vs PBO + MTX [a.]		17	12
95% CI for odds ratio		[3, 118]	[2, 80]
p-value [c.]		0.004	0.011
Odds ratio vs CZP 200 mg + MTX [b.]			1
95% CI for odds ratio			[1, 2]
p-value [c.]			0.9
Treatment by Region Interaction [d.] p-value = 0.50			
ACR-70 at Week 24			
Responder	1 (0%)	39 (16%)	26 (11%)
Odds ratio vs PBO + MTX [a.]		24	15
95% CI for odds ratio		[3, 176]	[2, 115]
p-value [c.]		0.002	0.008
Odds ratio vs CZP 200 mg + MTX [b.]			0.6
95% CI for odds ratio			[0, 1]
p-value [c.]			0.113
Treatment by Region Interaction [d.] p-value = 0.14			

Study 027 specified inhibition of progression of structural damage as a coprimary endpoint. Patients receiving certolizumab 400 mg and certolizumab 200 mg (0.2 units for both groups) experienced less radiographic progression over 52 weeks than patients receiving placebo (1.3 units) as measured by the change from baseline in the mTSS. The degree of inhibition compared to the placebo group was 92 and 85% with the certolizumab 400 and 200 mg doses, respectively, demonstrating that certolizumab exceeds the level of 75% inhibition that the Division has used to differentiate highly active agents that are described as "inhibiting" from less active agents that are described as "slowing" radiographic progression. Certolizumab reduced both components of the mTSS, namely the erosion component and the joint space narrowing component. Certolizumab treatment also increased the proportion of patients who had no measurable progression of structural damage over one year.

Table 8: Change from Baseline in mTSS at Weeks 24 and Week 52 – Study 027

Comparrison of Change from Baseline in mTSS at 52 Weeks Linear Extrapolation - ITT Population			
	PBO+MTX	CZP 200 mg sc q2w + MTX	CZP 400 mg sc q2w + MTX
	N = 199	N = 393	N = 390
Baseline mTSS			
n	199	391	389
Mean (SD)	39 (45)	38 (49)	38 (47)
Change from Baseline at Week 24			
n	180	353	355
Mean (SD)	1.3 (4)	0.2 (3)	0.2 (4)
Difference [a.] vs PBO + MTX (b.)		-0.5	-0.5
95% CI for Difference		[0.8, 0]	[-0.7,0]
p-value [c.]		<0.001	<0.001
% inhibition vs PBO+MTX [d.]		87%	83%
Change from Baseline at Week 52			
n	181	364	363
Mean (SD)	2.8 (8)	0.4 (6)	0.2 (5)
Difference [a.] vs PBO+MTX [b.]		-0.5	-0.6
97.5% CI for Difference		[-1.5, 0]	[-1.5,0]
p-value [c.]		<0.001	<0.001
% Inhibition vs PBO + MTX [d.]		85%	92%
Difference [a.] vs CZP 200 mg+MTX			0
95% CI for Difference			[0,0]
p-value [c.]			0.89

(a.) The differences are between CZP200/400 mg +MTX minus PBO+MTX.
(b.) Hodges-Lehman point estimate of shift and CI.
(c.) ANCOVA on the ranks with region and treatmetn as factors and rank Baseline as a covariate. Abbreviations: SD=standard deviation; PBO=placebo; MTX=methotrexate; CI=confidence interval. Revised from Table 11:14, page 118 of 8823 and Table 14.2.2:1, page 1360 of 8823.

Studies 027 and 050 assessed improvement in physical function based on the change in the Health Assessment Questionnaire – Disability Index (HAQ-DI). At baseline patients had moderately severe impairment in physical function (1.7 on the 0-3.0 unit scale). Patients treated with certolizumab experienced a greater reduction in HAQ-DI than patients receiving placebo (Table 9). The degree of improvement was 0.6 u, which exceeds the 0.22 u level that has been demonstrated to represent a clinically meaningful change.

Table 9: Health Assessment Questionnaire - Disability Index (HAQ-DI) - Study 027

Comparison of Change from Baseline in HAQ-DI - Study 027 Week 24 and Week 52 - LOCF (ITT Population)			
Visit Treatment	PBO+MTX N = 199	CZP 200 mg sc q2w + MTX N = 393	CZP 400 mg sc q2w + MTX N = 390
Week 24			
Baseline, Mean (SD)	1.7 (1)	1.7 (1)	1.7 (1)
Adj. Mean (SE)[a]	-0.2 (0)	-0.6 (0)	-0.6 (0)
Diff[b] vs PBO+MTX[a]			
Adj. Mean [95%CI][c]		-0.4 [-0.5, -0.3]	-0.4 [-0.5, -0.3]
P-value		<0.001	<0.001
Week 52			
Baseline, Mean (SD)	1.7 (1)	1.7 (1)	1.7 (1)
Adj. Mean (SE)[a]	-0.2 (0)	-0.6 (0)	-0.6 (0)
Diff[b] vs PBO+MTX[a]			
Adj. Mean [95%CI][c]		-0.4 [-0.5, -0.4]	-0.4 [-0.5, -0.4]
P-value		<0.001	<0.001
(a.) ANCOVA with region and treatment as factors and Baseline as covariate. (b.) The differences presented are CZP 200 mg/400 mg + MTX minus PBO+MTX. Abbbreviations: SE=standard error; CI=confidence interval; MTX=methotrexate; PBO=placebo. Revised from sponsor Table 11:16, page 125 of 8823 and Table 14.2.7:43, page 2116 of 8823.			

6.2.3. Other efficacy studies

None

6.2.4. Discussion of primary and secondary reviewers' comments and conclusions

The primary clinical review, Dr. Carolyn Yancey, concluded the studies had demonstrated efficacy of certolizumab for signs and symptoms of RA, for inhibition of progression of structural damage, for improvement in physical function and for inducing a major clinical response. She concluded that Study 027 demonstrated efficacy of the lyophilized formulation, which is the currently approved formulation and Study 050 demonstrated efficacy of the new formulation, namely prefilled syringes. She concluded that certolizumab at a dose of 400 mg q4wks was also efficacious both when given as monotherapy and when given in combination with MTX. I concur with Dr. Yancey's conclusions.

The biostatistics reviewer, Dr. Kate Meaker, also concluded that the studies had demonstrated efficacy of certolizumab for both the 200 mg q2wk maintenance dose and the alternative 400 mg q4wk maintenance dose. She concurred that the certolizumab monotherapy trial had demonstrated efficacy. Regarding labeling, Dr. Meaker recommended the results of the monotherapy trial not be included since the dose used was not the recommended regimen for marketing in order to avoid confusion with the Crohn's disease treatment regimen. (b) (4)

With respect to including the results of the monotherapy trial in product labeling, while it is true that the certolizumab dose regimen used in the monotherapy trial (Study 011) lacked the loading dose recommended for marketing it would nonetheless be of value to include some data in the label about the efficacy of monotherapy since that will be an

allowable mode of administration. Including some information about Study 011 would not overstate the efficacy of monotherapy since the available data suggest that the initial load increases the efficacy of the product. Another argument in favor of including data on monotherapy from Study 011 in the label is that those data would illustrate the more favorable results seen with MTX combination therapy as compared to monotherapy. I concur with Dr. Meaker's recommendation [redacted] (b) (4)

6.2.5. Pediatric use/PREA waivers/deferrals

Currently there are two approved TNF blockers for treatment of children with polyarticular juvenile idiopathic arthritis (JIA): the soluble TNF receptor fusion protein etanercept (Enbrel) and the anti-TNF monoclonal antibody adalimumab (Humira). The RA guidance document states that efficacy results from adults can be extrapolated to children with the polyarticular form of JIA. Based on the Pediatric Rule, given the rationale for the ability to extrapolate adult efficacy data to children and the previous demonstration that two other products in the class show efficacy in children a case can be made that efficacy studies should not be required for certolizumab. This recommendation is consistent with the recent decision to use extrapolation of adult data to children for Cimzia for Crohn's disease and, therefore, to not require randomized efficacy studies. However, safety and PK studies should be required in children as well as careful studies of immunogenicity. These issues were presented to the Pediatric Review Committee (PeRC) and they concurred that an efficacy study is not required. Based on the prevalence of polyarticular JIA in children of different ages the Applicant should be granted a deferral of studies in the 2-17 year age group and a waiver for the 0-2 year age group.

6.2.6. Discussion of notable efficacy issues

There are no notable efficacy issues.

6.3. Safety

6.3.1. General safety considerations

Currently there are three approved TNF blockers for RA: etanercept (Enbrel), infliximab (Remicade) and adalimumab (Humira). While there are some individual differences between these products in their safety profiles in general terms the safety issues are common to the class. These include infection risk, including reactivation of latent tuberculosis infection and opportunistic infections, risk of malignancy, risk of demyelinating disease and uncommon occurrence of autoimmune disease. While these are serious risks these events are uncommon and the benefits of TNF blockers are believed to outweigh the potential risks. For certolizumab the safety profile was found to be similar to what would be expected for a novel TNF blocker with the major safety signal being tuberculosis.

The size of the safety database of certolizumab in RA was adequate. It exceeded by a large margin the minimum guidelines for products intended for chronic use contained in the ICH E1 guidance document. Overall, the safety database in the RA clinical

development program consisted of a total of 2367 patients treated with CZP at the doses recommended for marketing, including 2204 treated for 3 months or longer, 2030 treated for 6 months or longer and 1663 treated for 12 months or longer (Table 10). Patients studied in the certolizumab clinical development program were representative of the general RA population in demographic features and their level of disease activity. Many of the patients in the safety database were receiving the widely used disease modifying anti-rheumatic drug (DMARD) MTX although patients were excluded who were receiving concomitant biologic DMARD's.

Table 10: Extent of Exposure: All Doses in All Studies in RA – Safety Population

Extent of Exposure: All CZP Doses (OL and PBO-Controlled studies) in RA					
	PBO N=647	CZP 200 mg q2w N=640	CZP 400 mg q2w N=1487	CZP 400 mg q4w N=513	All CZP Doses N=2367
Duration of Expos. (days)					
Mean (SD)	127 (73)	226 (117)	357 (162)	794 (514)	497 (324)
Min, Max	14, 366	14, 369	14, 714	28, 1543	14, 1543
Total Exposure (Pt.-Yrs.)	225	396	1453	1116	3,218
Duration of Exposure					
< 3 months	179 (28%)	35 (6%)	61 (4%)	67 (13%)	163 (7%)
≥ 3 to < 6 months	418 (65%)	342 (53%)	124 (8%)	28 (6%)	174 (7%)
≥ 6 to < 12 months	8 (1%)	12 (2%)	577 (39)	65 (13%)	367 (16%)
≥ 12 to < 18 months	42 (7%)	251 (39%)	478 (32%)	46 (9%)	846 (36%)
≥ 18 to < 24 months	0	0	247 (17%)	25 (5%)	535 (23%)
≥ 24 months	0	0	0	282 (55%)	282 (12%)
≥ 12	42 (7%)	251 (39%)	725 (49%)	353 (69%)	1663 (71%)

6.3.2. Safety findings from submitted clinical trials

In the Integrated Summary of Safety, the Applicant reported that 9 of the 1774 certolizumab-treated patients (0.5%) died in the placebo-controlled trials, compared to 1 of 647 placebo-treated patients (0.2%). In the Applicant's analysis 6 of the 9 deaths in the certolizumab group were due to cardiovascular events, none to infections and 1 each to three other categories. Although patients with RA do have an increased risk of death of cardiovascular causes this preponderance of cardiovascular deaths is unusual in RA clinical trials. To investigate the causes of death further the clinical reviewer examined the individual patient narratives and determined that most of the deaths of cardiovascular causes (4 of 6) were actually infectious in nature. Thus the FDA analysis attributes 2 deaths to cardiovascular causes and 5 to infections. This distribution of causes of death is more typical of an immunosuppressive product. However, there remains the question of how the observed mortality rate with certolizumab compares to the expected rate.

To better understand the rate of mortality among certolizumab-treated patients a number of analyses were carried out. First to compare the mortality rate with certolizumab to the rate with placebo it is important to adjust for the longer duration of exposure in the certolizumab group, owing to the early escape provision that was more frequent in the placebo group. As shown in Table 11, when adjusted for the duration of exposure deaths in the certolizumab group occurred at a rate of 0.94/100 pt-yrs compared to 0.44/100 pt-yrs in controls. Given the very small number of events seen in the control group (one

event) it is difficult to draw firm conclusions. The mortality rate was next examined in the total RA safety database, including long-term open-label treatment studies. In the total database the rate of death was 0.822/100 pt-yrs. In contrast, the expected rate of death based on mortality rates in the general population is 0.804. These data taken together do not indicate an increased mortality rate in patients treated with certolizumab. Overall, the causes of death in the entire safety database were typical of those expected in an RA population.

Table 11: All Cause Mortality in PBO-Controlled CZP RA Studies

Summary Table - All Cause Mortality CZP Placebo Controlled RA Clinical Studies Program					
[Studies CZP-002 (iv); CZP-004, -011, -014, -027, -050 (sc); N=1774] **Comparison to Mortality Rates in the Population Exposed to CZP** **1 Death: PBO-Controlled Group ; 9 Deaths: CZP Treatment Groups** Distribution of Cause of Death in Patients Exposed to CZP					
	Number of Observed Cases				
	PBO+ MTX	CZP Doses 200 mg, 400 mg q2w+MTX; 400 mg q4w	Reviewer All CZP Doses	Sponsor All CZP Doses	Expected # of Cases [(a)]
PBO-Controlled CZP Treatment Group	N=647		N=1774	N=1774	
Cause of Death					
Cardiovascular		2	2	6	10
Infection		5	5	0	1.2
Malignancies		1	1	1	8.4
Injuries (fem frx shock)		1	1	1	2.8
Other non-communicable diseases			0	1	4.6
CZP Treated Patients: TOTAL			9	9	
PBO-Controlled Treatment Group					
Cause of Death					
Cardiovascular	1				
PBO Treated Patients: TOTAL	1				N.A.
OVERALL TOTAL			10	10	
Exposure in Placebo-Controlled Studies					
Total Expo. CZP/ PBO-Contr.	957.4 pt-yrs.				
Deaths per 100pt-yrs.	0.94				
Total Expos. PBO-Contr.	224.9 pt.-yrs.				
Deaths per 100pt-yrs.	0.44				
(a.) The number of deaths is compared to the proportion expected in the general population from the World Health Organization (WHO) Burden of Disease database. The crude rates have been adjusted for age, gender, and region from the 2001 data. Table revised from sponsor Table 3:3, page 11 0f 27, Mortality Report.					

Table 12: Incidence of Mortality in RA Patients Exposed to CZP in PBO-Controlled Studies

Incidence of Mortality in RA Patients Exposed to CZP PBO-Controlled Studies						
	PBO-Controlled Studies					All Pts. in CZP RA Studies
	PBO	CZP 200 q2w+MTX	CZP 400 q2w+MTX	CZP 400 q4w	All CZP Doses (PBO-Cont.)	
Total # Patients	**N = 647**	**N = 640**	**N = 635**	**N = 278**	**N = 1774**	**N = 2367**
Total # Deaths (%)	**1 (0.15%)**	**4 (0.6%)**	**5 (0.78%)**	**0**	**9 (0.5%)**	**25 (1.1%)**
Total Exposure, pt.-yrs.	225	396	410	107	957	3284
Deaths per 100 pt.-yrs.	0.44	1	1.2	0	0.94	0.822
Global Mortality Rate in 100 pt-yrs (CZP RA Studies)						0.822
Weighted Mean Mortality Rate in 100 pt-yrs (General Population)						0.803

A higher rate of serious adverse events was observed among certolizumab-treated patients (11%, 20 per 100 pt-yrs) compared with placebo controls (7%, 18 per 100 pt-yrs) in the randomized trials. Infections were the most important cause of higher serious adverse event rates in the certolizumab group (4% vs. 0.6% with placebo), including tuberculosis, lower respiratory tract infections, bacterial infections and upper respiratory tract infections.

Tuberculosis (TB) is a concern with the class of TNF blockers. The labels for the approved TNF blockers recommend screening and prophylaxis for latent TB infection before receiving a TNF blocker. TB also appears to be a concern with certolizumab. Overall 9 patients developed TB with certolizumab in the randomized trials (0.5%) as compared to none in the placebo arms. Overall, including both randomized trials and long-term extension trials, a total of 26 cases of TB were observed in the RA clinical development program for certolizumab (Table 13). None were in the US or North America. The vast majority were among patients from Eastern Europe (23 of 26 cases). During the clinical trials patients were screened with a PPD skin test prior to study enrollment and patients testing positive were treated with anti-tuberculosis drugs before receiving certolizumab. These results suggest that in areas highly endemic for latent tuberculosis infection, such as Eastern Europe, standard procedures for screening and prophylaxis are not adequate to prevent cases of tuberculosis.

Table 13: Cases of Tuberculosis in All CZP Clinical Development Programs

Number of TB Cases by Region and Indication (as of July 2007)				
	Crohn's Disease	Rheumatoid Arthritis	Psoriasis	Total
# Unique Patients	2,508	2,367	117	5,118
Total exposure (pt.[a]-yrs.)	2286.3 (2287.9[a])	3997.6 (4000.5[a])	97 (97[a])	6404.8 (6409.3[a])
North America	0	0	0	0
Western Europe	1	2	1 *	4
Eastern Europe	0	23 **	0	23
Japan	1	0	0	1
South Africa ***	5	0	0	5
Rest of the World	1	1 *	0	2
Total	8	26	1	35 (14 *)

Sponsor Table 9:1 and 9:2, page 14 and 13 of 62, Risk of TB with CZP Global Health Outcomes Research.
a. Total exposure for confirmed cases only Expsoure by Region.
* Confirmed cases.
** 12 of 23 cases from Eastern Europe were confirmed cases.
*** South Africa is shown as a separate region in this table yet is part of the Rest of the World for all other tables.

In addition to the serious infections the overall rate of infections was higher in the certolizumab group (38% vs. 23%, unadjusted for differing durations of exposure). In general, the types of infections were typical of those seen in the general RA population and included upper respiratory tract infections, nasopharyngitis, urinary tract infections and lower respiratory tract infections.

Malignancies are a concern with certolizumab because of its immunosuppressive mechanism of action and data for other TNF blockers suggesting a possible increased rate in certain patient populations. Overall the rate of malignancies was not increased in certolizumab-treated patients compared to the expected rate. A total of three lymphoma cases were observed with a standardized incidence ratio (SIR) of 4.97 [95% CI: 1.03 to 14.54]. Given that the rate of lymphoma is increased in RA patients compared to the general population and that the risk of lymphoma is particularly increased in patients with highly active disease a higher rate of lymphoma is not unexpected. An SIR of 4.97 is within the range that has been observed previously in patients receiving other TNF blockers.

Exploration of common adverse events, discontinuations due to adverse events or laboratory abnormalities did not reveal additional safety signals.

One aspect of laboratory evaluations calls for additional comment. Patients treated with other TNF blockers have developed autoantibodies (antinuclear antibodies (ANA's) and anti-dsDNA antibodies) more frequently in clinical trials than controls. The rate of conversion to autoantibody positivity varies depending on the specific product. The majority of patients developing autoantibody positivity have no clinical adverse outcomes; however, clinical autoimmunity has developed in a small number. In their analysis of the autoantibody data the Applicant contends that only a very small number of patients convert to autoantibody positivity. However, the data submitted do not support this conclusion. With the assays for ANA and anti-dsDNA used in the Phase 3 studies

027 and 050 the majority of patients were positive at baseline. This is highly unusual in this patient population and suggests there was a problem with the assay.

In summary, the major safety concern observed with certolizumab treatment was an increased risk of serious infections, in particular tuberculosis. Tuberculosis was a particular concern in highly endemic areas, such as Eastern Europe.

6.3.3. Safety update

Review of the safety update identified no new safety concerns.

6.3.4. Immunogenicity

Antibodies to certolizumab developed in some treated patients (Table 14). Overall the rate of immunogenicity was lowest in patients receiving the highest dose tested, namely 2% in the certolizumab 400 mg q2wk plus MTX group. The rate was higher in patients receiving the dose proposed for approval, namely 10% in the certolizumab 200 mg q2wk group. The rate of immunogenicity was also higher in patients receiving certolizumab monotherapy, namely 22%. Efficacy was diminished in patients developing anti-certolizumab antibodies. These results suggest that administering certolizumab in combination with MTX would reduce immunogenicity and that monotherapy would be associated with less clinical benefit. In contrast, the somewhat higher rate of immunogenicity with the 200 mg q2wk regimen as compared to the 400 mg q2wk regimen, as shown in Studies 027 and 050, did not translate into lower levels of clinical response. This lesser effect of anti-certolizumab antibodies in Studies 027 and 050 may be related to lower titers of antibodies seen with the treatment regimens used in those studies, i.e., the presence of the initial load and the concomitant use of MTX.

Table 14: Anti-CZP Antibody Positive Patients in CZP RA Studies

Anti-CZP Antibody Positive Patients - Study 011, 014, 027 and 050 in RA					
	CZP 200 mg [(a.)] sc q2w + MTX N = 640	CZP 400 mg sc q2w + MTX N = 633	CZP 400 mg sc q4w + MTX N = 124	CZP 400 mg sc N = 111	All CZP Doses N = 1508
Antibody Positive	63 (10%)	12 (2%)	5 (4%)	25 (22.5%)	105 (7%)

6.3.5. Discussion of primary reviewer's comments and conclusions

The primary reviewer, Dr. Yancey, concluded that the safety database includeded an adequate exposure to assess the safety of certolizumab in patients with RA. She concluded after careful review that the mortality rate in the randomized and long-term extension trials was not elevated compared to that expected in patients with RA. She observed that the rate of serious adverse events was higher with certolizumab than with controls and that the higher rate of SAEs was attributable to infections. One particular serious infection seen more frequently in certolizumab-treated patients than in controls was tuberculosis (TB). This is consistent with the experience with the approved TNF blockers, where cases of reactivation of latent tuberculosis infection have been observed, particularly with TNF-blocking monoclonal antibodies. In the certolizumab clinical

development program all the cases of TB were seen in sites outside North America, consistent with the higher underlying rates of latent tuberculosis infection seen in the countries where the studies were conducted, particularly in Eastern European countries.

Dr. Yancey concluded that the overall rate of malignancies in the certolizumab safety database was not increased compared to the expected rate. However, the rate of lymphomas was increased compared to the expected rate in the general population (4.97 relative risk). Unfortunately, data are not available on the rate of lymphoma in the RA population so it is not possible to conclude that certolizumab treatment increases the risk of lymphoma. In fact, the relative risk of lymphoma seen with certolizumab compared to the general population is in the same range as has been observed with other TNF blockers in RA, e.g., infliximab and adalimumab. A higher rate of lymphoma has been observed in patients with RA not taking TNF blockers and is particularly elevated in patients with highly active RA. Several epidemiologic studies have shown that while patients with RA do have an elevated risk of lymphoma that risk is similar in patients receiving TNF blockers and patients who are not receiving TNF blockers.

Dr. Yancey also noted that some patients receiving certolizumab develop autoantibodies (anti-dsDNA and ANA) and that some patients developed a lupus-like syndrome. Development of autoantibodies and lupus-like syndrome have also been associated with the approved TNF blockers.

In summary, Dr. Yancey identified serious infections, particularly tuberculosis, as the major safety concern with certolizumab. Overall, she concluded that the safety profile of certolizumab was similar to that observed with other TNF blockers and similar to what is currently in the Cimzia label. I concur.

6.3.6. Discussion of notable safety issues

Overall the major safety concern with certolizumab is uncommon but serious infections. In general, the safety profile is similar to what is observed with the other approved TNF blockers.

An additional safety issue arose during the review of the submission by DMEP in OSE. DMEP was concerned about the fact that if the current submission is approved that there would be a lyophilized product available for Crohn's disease and a liquid product available in prefilled syringes for patients with RA. DMEP was concerned that if a patients with RA got a package with the lyophilized formulation that they would not know how to administer it. A teleconference was held with the Applicant to discuss this issue and a proposal for resolution was discussed. The proposal involves the inclusion of instructions for administration to accompany each kit. (b) (4) DMEP agreed that this plan would address their concerns.

7. Advisory Committee Meeting

Since the safety and efficacy data for certolizumab appear similar to what has been observed with other products in this class no advisory committee was deemed necessary.

8. Financial Disclosure

No potentially conflicting financial interests were identified.

9. Labeling

9.1. Physician labeling

At the time of completion of this CDTL memo, detailed consideration of the label was ongoing. The label should contain sufficient information on response rates with certolizumab monotherapy and with q4wk dosing that prescribers can see that although these regimens provide efficacy the efficacy is not as high as with the q2wk dosing and with use in combination with MTX. The rate of immunogenicity with different dose regimens should also be included. Finally, the description of autoantibody formation should be modified compared to that proposed by the Applicant because of the very high background rate of autoantibody positivity.

10. DSI audits

DSI inspected study sites in Slovakia and in Russia. At the time of writing of this memo the final DSI review had not been completed. However, an e-mail from DSI dated 8/21/08 indicated that the inspection report from the Slovakian site was acceptable and that the inspection of the Russian site appeared acceptable as well.

11. Conclusions and recommendations

11.1. Regulatory action

Data from four adequate and controlled trials support the efficacy of certolizumab in patients with rheumatoid arthritis. Two trials studied the efficacy of the proposed dose regimen consisting of an initial loading dose of 400 mg SC q2wks x3 followed by certolizumab 200 mg q2wks in combination with MTX. These trials showed ACR20 response rates at 6 months of approximately 60% compared to placebo response rates of 14%. The studies also showed inhibition of progression of structural damage over 12 months with rates of progression reduced by approximately 85% compared to placebo controls. Patients treated with certolizumab also experienced greater improvement in physical function than controls and more frequently achieved Major Clinical Responses. Certolizumab was demonstrated effective when used with MTX and when used as monotherapy. While the 200 mg q2wks dose regimen showed higher response rates the 400 mg q4wk dose regimen was also efficacious.

The safety profile of certolizumab is similar to that of other TNF blocking agents. The main safety concern is serious infection.

One unresolved issue concerns the amount of [redacted] (b) (4) that may be present in the product. So long as the final DSI inspection results show no additional deficiencies, an acceptable REMS is agreed upon, labeling and post-marketing requirements can be agreed upon with the Applicant, [redacted] (b) (4) can be resolved in an acceptable manner, certolizumab should be approved for the treatment of moderately to severely active rheumatoid arthritis.

11.2. Safety concerns to be followed postmarketing

The major safety concerns that should be followed postmarketing are those known to be associated with immunosuppressive agents in RA, including serious infections, autoimmune diseases, malignancies and demyelinating events.

11.3. Risk Evaluation and Mitigation Strategy (REMS)

11.3.1. General considerations on the need for, and goals of, any REMS beyond standard labeling and pharmacovigilance

Cimzia currently has a Medication Guide and a REMS. The REMS is in the process of being modified because of the recent identification of a class issue involving all TNF blockers, namely the occurrence of cases of histoplasmosis that is not promptly recognized by clinicians. The REMS is to be modified to communicate concerns regarding histoplasmosis to clinicians and to monitor whether physicians are becoming more aware of the possibility of histoplasmosis in patients at risk. As of the time of writing of this memorandum the REMS for the Crohn's disease indication had not been approved. It is expected to be approved shortly. When Cimzia is subsequently approved for the rheumatoid arthritis indication the REMS should be reviewed to make sure it includes communication of the appropriate safety information to rheumatologists.

11.4. Postmarketing studies

11.4.1. Required studies

Generally, when the Agency has approved new immunosuppressive products for RA the action has been associated with postmarketing commitments/requirements to carry out long-term, open-label treatment trials in approximately 1000-1500 patients for 5 years to explore long-term safety. The Agency has also expected applicants to study the effects of the product on the ability to mount responses to therapeutic vaccination. The Agency has not mandated registry studies in adult RA. However, registries of all the approved biologics have been set up in Europe (UK, Sweden, Germany and other countries) and in the US (Dr. Fred Wolfe's National Data Bank for Rheumatic Diseases (NDB) and the Consortium of Rheumatology Researchers of North America (CORRONA)). Although these registries have not generated new safety signals data from the registries have been very useful in further characterizing safety signals that were identified through other means (e.g., spontaneous adverse event reports).

One important issue to consider for certolizumab is whether to require long-term open-label treatment studies of safety and whether to require a registry. Currently a great deal of information is available on the safety profile of TNF blockers with long-term use. The data on safety of TNF blockers is derived from long-term open-label treatment studies of the approved TNF blockers and from registries both in the US and in Europe. Five-year data are available on patients treated with etanercept and with adalimumab and studies are ongoing out to 10 years. As the fourth TNF blocker to be approved for RA it is unclear what additional information would be derived from long-term open-label treatment studies or from additional registries studies with certolizumab. It is the opinion of this reviewer and of the primary reviewer that adequate data are available on long-term use of TNF blockers and that the Applicant need not be required to conduct additional long-term treatment studies or registries in adult patients with RA. However, OSE has reviewed the issue and believes that a long-term registry should be required of the Applicant. In a discussion with Dr. Iyasu, he explained that there is an effort underway to utilize administrative databases in the future to better characterize postmarketing safety of new products. However, those initiatives are not fully in place at the current time. Given that there remain some safety issues with TNF blockers that have not been fully characterized (e.g., the degree to which they increase the risk of serious infections and the question as to whether they increase the risk of malignancy), it is OSE's recommendation that a registry be undertaken to further characterize the safety of Cimzia postmarketing. While I have questions about what specific new information will be provided by such a registry I concur that a registry is a reasonable additional tool to further characterize the safety of Cimzia.

In summary, the Applicant should be required to conduct a long-term registry study in adults patients with RA and to conduct a study in children with JIA ages 2-17 to collect PK, safety and immunogenicity information.

11.4.2. Commitments (PMCs)

No additional clinical PMC's are necessary. The Applicant should commit to carrying out the two CMC-related PMC's discussed in section 3.1 above.

11.4.3. Other agreements with Sponsor

None.

Cross-Discipline Team Leader Memo

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation 2
Division of Anesthesia, Analgesia and Rheumatology Products

Cross-Discipline Team Leader Memorandum

Date: September 6, 2008

To: File, BLA 125271/0

From: Jeffrey Siegel, M.D. Jeffrey N. Siegel 9/6/08
Clinical Team Leader
ODE2 - Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Re: BLA 125271/0
CIMZIA® (certolizumab pegol)
UCB, Inc.
Proposed indication: Rheumatoid arthritis

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1. Introduction to Review

UCB submitted this biologic licensing application (BLA) seeking the approval of certolizumab pegol (CZP) for the treatment of patients with rheumatoid arthritis (RA). CZP is a PEGylated monoclonal antibody Fab' fragment that binds to tumor necrosis factor-α (TNF), thereby inhibiting its biologic activity. CZP is currently approved for the treatment of Crohn's disease. The Applicant submitted data from four Phase 3 trials of CZP in RA. Two trials used the dosing regimen recommended for approval in combination with methotrexate (MTX) and included every 2 week dosing and an initial loading dose. The other two trials were conducted earlier and used every 4 week dosing and no initial loading dose: one investigated CZP monotherapy; the other combination therapy with MTX. Overall, the safety database in the RA clinical development program consisted of a total of 2367 patients treated with CZP at the doses recommended for marketing, including 2204 treated for 3 months or longer, 2030 treated for 6 months or longer and 1663 treated for 12 months or longer. The Applicant proposes administration of CZP subcutaneously beginning with a loading dose of 400 mg every 2 weeks for 3 doses followed by 200 mg every 2 weeks.

During the review of this application, important issues arose regarding product quality, clinical pharmacology, clinical efficacy and clinical safety, OSE review of the proposed packaging, what studies should be required under PREA and the need for a postmarketing registry. The product quality issues involve assurance that the levels of the genotoxic (b) (4) in the product are adequately low. The Clinical Pharmacology and clinical efficacy issue concerns immunogenicity of the product when given as monotherapy and efficacy of every 4 week dosing. The clinical safety issue involved an apparent excess of cardiovascular deaths in the certolizumab pegol arms of the randomized trials in the Applicant's submission. The OSE concern related to the potential for confusion if the new prefilled syringe formulation and the older lyophilized formulations are both marketed at the same time. The issue concerning PREA was whether an efficacy trial should be required in children with juvenile idiopathic arthritis (JIA). The issue concerning a postmarketing registry is whether the Applicant should be required to conduct a registry to assess safety of certolizumab given that it is the fourth product in this class for RA. At the time of this review most of these issues have been adequately addressed. The issue concerning (b) (4) is in the process of being addressed as are the issues concerning requirements under PREA and the need for a postmarketing registry. This memo will review the regulatory background for this application, the evidence supporting efficacy and safety of tocilizumab in RA and key findings in other disciplines.

2. Background – Regulatory history

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory condition that primarily affects the joints but can also affect other organs. Active RA is associated with pain and physical impairment. If left untreated or inadequately treated RA leads to progressive damage to joints with subsequent disability and the need for joint replacement. The FDA Guidance for Industry on clinical development programs for RA

(RA guidance document) describes the types of clinical trials needed for approval of products for RA. The basic claim usually assessed in clinical trials for approval is improvement in signs and symptoms as measured by an accepted composite index such as the ACR 20 (American College of Rheumatology 20). Claims describing additional benefits that can be assessed in clinical trials include improvement in physical function, major clinical response, inhibition of progression of structural damage, complete clinical response and remission. In addition to the basic claim of treatment of signs and symptoms of RA, the Applicant is seeking claims of improvement in physical function, major clinical response and inhibition of progression of structural damage.

The drug development program for certolizumab in RA began with a Phase 2, dose-finding trial followed by two Phase 3 trials (Studies 011 and 014). Those studies met their primary efficacy endpoint of ACR 20 response at 6 months; however, the Applicant noted that the indicators of more substantial clinical response, ACR 50 and 70, were lower than has been observed with other TNF blockers and the ACR 20 responses were somewhat lower as well. Therefore, the Applicant met with the Agency in October, 2004, to discuss plans for conducting two additional Phase 3 trials to explore an alternative dosing regimen that added an initial load and more frequent, every other week, dosing. After completion of those additional Phase 3 studies (Studies 027 and 050) the Applicant submitted a biologic licensing application (BLA) for certolizumab pegol (Cimzia) for the treatment of rheumatoid arthritis. At the same time the Applicant had submitted a BLA for approval of certolizumab pegol for treatment of Crohn's disease. That BLA was approved in April, 2008.

3. CMC/Microbiology/Device

3.1. General product quality considerations

Certolizumab pegol is already approved and marketed as a lyophilized powder. For the current submission the Applicant submitted data to support their proposal to market a liquid formulation in prefilled syringes. Review of liquid certolizumab pegol in prefilled syringes by the product quality review team found no issues that would prevent the approval of this new dosage form. The Pharmacology/toxicology review team raised concerns about the possibility of there being (b) (4) in certolizumab. This issue will be addressed further under section 4.

3.2. Facilities review/inspection

At the time of writing of this memorandum the facilities inspection had yet not been carried out. It is scheduled for September, 2008.

4. Nonclinical Pharmacology/Toxicology

Review of the pharmacology/toxicology section of the application revealed no issues that would prevent approval. However, the pharmacology/toxicology reviewer expressed concern about the lack of information about the levels of (b) (4) present in the drug product and drug substance. (b) (4)

polyethylene glycol (PEG). [redacted] (b) (4) is a toxic substance that is also genotoxic and is a reproductive toxin. The review team is planning to obtain additional information from the Applicant about levels of [redacted] (b) (4) in drug substance and drug product. Depending on the information provided there may be a need for further risk assessment and for setting specification levels.

5. Clinical Pharmacology/Biopharmaceutics

5.1. General clinical pharmacology/biopharmaceutics considerations

The PK of certolizumab was similar in healthy volunteers and RA patients. Mean clearance values were 0.13 - 0.20 ml/hr/kg with a mean terminal phase half-live of 13 – 15 days. The volume of distribution was similar to total blood volume (60 – 102 ml/kg). Bioavailability of subcutaneously administered certolizumab was approximately 80%.

Exposure-response modeling indicated that optimal ACR 20 responses were associated with trough certolizumab levels of 10 mcg/mL. The proposed load allows steady state levels to be achieved more quickly. The mean trough level for patients receiving the proposed dose regimen exceeded the threshold of 10 mcg/mL; however, more patients achieved trough levels of 10 mcg/mL in the 400 mg q2wk arm than in the 200 mg q2wk arm. The proposed alternative dose regimen of 400 mg q4wk is associated with lower trough levels with exposure-response modeling, suggesting that the likelihood of achieving an ACR20 response is reduced from 70% to 50% with the q4w regimen as compared to the q2wk regimen. Based on the expectation of lower trough levels and predicted lower ACR20 responses the Clinical Pharmacology review team believes that the alternative 400 mg q4wk regimen is inappropriate. For labeling the review team suggests that the 400 q4wk regimen be recommended only for patients receiving concomitant MTX.

Some patients receiving certolizumab pegol developed anti-product antibodies. Patients who developed anti-certolizumab antibodies had lower blood levels of certolizumab due to increased clearance and were less likely to have a clinical response. The likelihood of developing anti-certolizumab antibodies was increased in patients who received certolizumab monotherapy compared to patients receiving certolizumab in combination with methotrexate (MTX). For labeling the Clinical Pharmacology review team suggests that certolizumab be recommended for use with MTX and that monotherapy be recommended only for MTX-intolerant patients.

Population PK analysis evaluated the effect of age, body weight, race, gender, anti-certolizumab antibody status, concomitant medications (methotrexate, glucocorticoids, NSAIDs, other DMARDs) and laboratory assay on the PK of certolizumab. The analysis identified body weight and antibody status as important covariates influencing clearance, with antibody status being the major contributor to variability in clearance. Despite the influence of body weight on the PK of certolizumab, the Clinical Pharmacology review team concluded that fixed dosing is appropriate since the probability of ACR20 response is similar (~70%) across all body weight quartiles due to the shallow body weight – C_{trough} relationship and high enough exposures at the proposed dosing regimen

5.2. Drug-drug interactions

Since immunoglobulin molecules are not metabolized by P450 enzymes, direct pharmacokinetic interaction via the CYP pathway is not expected between certolizumab and small molecules. Hence, formal drug-drug interaction studies were not conducted and they were not considered necessary. Studies of MTX pharmacokinetics were carried out in patients receiving certolizumab pegol and showed no significant effect on MTX pharmacokinetics. As described above, MTX coadministration did have an important effect on certolizumab blood levels by reducing the likelihood of developing anti-certolizumab antibodies.

5.3. Pathway of Elimination

For antibodies such as certolizumab, two types of pathways mediate elimination mechanisms: a nonspecific linear clearance by the reticuloendothelial system and an antigen-mediated saturable clearance.

5.4. Demographic interactions/special populations

Population PK studies that evaluated the effect of age, race and gender found no significant interactions. No information was submitted on PK in children. The Applicant has requested a deferral for pediatric studies.

5.5. Thorough QT study or other QT assessment

The effects of certolizumab on QT were not formally assessed as biologic products like certolizumab are generally not expected to interact with cardiac ion channels.

5.6. Notable issues

None.

6. Clinical/Statistical

6.1. General Discussion

The Applicant submitted results of four Phase 3 trials of efficacy and safety in patients with RA. In general, the Applicant followed advice provided by the Agency in the End of Phase 2 meeting on the design and analysis of the clinical trials and on acquiring adequate data to assess safety. All patients had established disease and most had an incomplete response to MTX. The Applicant submitted data to support a signs & symptoms claim as well as claims of inhibition of progression of structural damage, improvement in physical function and major clinical response. Significant issues regarding efficacy include whether the efficacy is adequate with monotherapy and with 400 mg q4w dosing to recommend these dose regimens. Significant safety issues include the disproportionate number of deaths reportedly due to cardiovascular disease in the certolizumab arms in the submission and the large number of cases of tuberculosis despite screening and treatment for latent tuberculosis infection in patients who screened

positive. Review of the reports of deaths of cardiovascular disease in the certolizumab arms revealed that most of these patients actually had an infectious etiology and that the cardiovascular event was a secondary event. An increased risk of infection is an expected event for certolizumab based on its immunosuppressive mechanism of action and on prior experience with other products in this class.

6.2. Efficacy

6.2.1. Dose identification/selection and limitations

The Applicant conducted an initial dose-finding study in which patients received placebo or study drug SC every 4 weeks x3 at doses of 0 (placebo), 50, 100, 200, 400, 600 or 800. ACR20 responses at week 12 were 15%, 21%, 20%, 34%, 60%, 64%, and 79%, respectively. Based on these findings the Applicant carried out their two initial Phase 3 studies using a dose of 400 mg SC q4wks. Study 011 was a randomized, placebo-controlled trial of certolizumab monotherapy in patients with active RA. Study 014 had a similar design but studied certolizumab treatment as add-on to background stable doses of MTX. As shown in Table 1 (this and all other tables and figures copied from the clinical review by Dr. Carolyn Yancey), treatment with certolizumab 400 mgSC q4wk was associated with an increase in the proportion of patients achieving the primary endpoint, the ACR20. However, relatively few patients achieved the higher level ACR 70 response (Table 2). In contrast to the 6% of certolizumab-treated patients achieving an ACR 70 response in Study 011 the proportion of patients achieving similar levels of response in studies of other TNF blockers has been in the mid-teens. Similarly, in Study 014 of certolizumab in combination with MTX ACR20 responses were observed but no ACR 70 responses.

Table 1: ACR20 Response at Week 24 – Study 011

ACR20 Response at Week 24 - Primary Analysis - Study 011 (mITT Population)			
	PBO N = 109	CZP 400 mg sc q4w N = 111	p-Value [a.]
Responder [b.]	10 (9%)	50 (46%)	<0.001

(a.) Cochran-Mantel-Haenszel (CMH) test of treatment comparison stratified by country.
(b.) A patient was considered a responder if he/she met the criteria of ACR20 improvement over Baseline at Week 24. Any patient who withdraws from the study at any time for any reason was considered a non-responder. Revised from sponsor Table 14.2.1:1, page 428 of 5470.

Table 2: ACR70 Response at Week 24 – Study 011

ACR70 Response at Week 24 - Study 011 (mITT population)			
Week 24	PBO N = 109	CZP 400 mg q4w N = 111	p-value
Responder [a.]	0	6 (6%)	0.013

Table 3: Primary Endpoint Analysis and Sensitivity Analyses, ACR20 Response – Study 014

ACR20 Response at Week 24 - Study 014			
Sensitivity Analysis (mITT)			
	PBO + MTX N = 119	CZP 400 mg sc q4w + MTX N = 124	p-Value [a.]
Responder [b.]	32 (27%)	59 (48%)	<0.001
Sensitvity Analysis - Excuding Protocol Violators (mITT)			
Responder [b.]	21 (27%)	45 (50%)	0.002
Sensivity Analysis - Excluding CZP Treated Protocol Violators (mITT)			
Responder [b.]	27 (23%)	45 (50%)	<0.001

(a.) Cochran-Mantel-Haenszel (CMH) test of treatment comparison stratified by country.
(b.) A patient was considered a responder if he/she met the criteria for ACR20 improvement over Baseline at Week 24. Any patient who withdrew was considered a non-responder.
Abbreviations: PBO=placebo; MTX=methotrexate; mITT= modified intent-to-treat.
Revised from sponsor Table 14.2.1:2, page 443 of 6006.

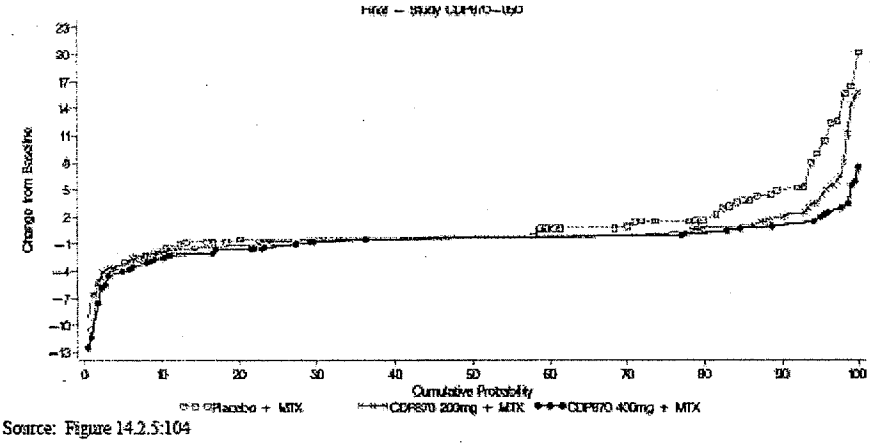
Table 4: ACR50 and ACR70 at Week 24 – Study 014

ACR50 and ACR70 at Week 24 - Study 014 (mITT)			
	PBO + MTX (N=119)	CZP 400 mg q4w + MTX (N=124)	p-value [a.]
ACR-50			
Week 24, Responder	7 (6%)	22 (18%)	0.004
ACR-70			
Week 24, Responder	2 (2%)	0	0.133

While the results from Studies 011 and 014 suggest that certolizumab 400 mg SC q4wk is efficacious, it also appears to be a suboptimal dose. After completing Studies 011 and 014, the Applicant made two changes to the dose regimen for certolizumab for the subsequent studies. They added an initial load consisting of 400 mg SC q2wk x3 and changed the dosing interval to q2wks for maintenance dosing. As will be described in more detail in section 6.2.2 these later studies (027 and 050) showed efficacy of certolizumab 200 mg q2wks and 400 mg q2wks and achieved response rates similar to what has been seen with other TNF blockers.

Detailed examination of the results of Studies 027 and 050 suggest that overall the efficacy of the 200 mg and 400 mg SC q2wk doses are similar. However, there are a few findings indicating that the 400 mg dose may be slightly better. Although the ACR response rates were similar for the 200 mg and 400 mg SC q2wk doses, the 200 mg dose was more immunogenic. In Study 027, 11% of patients receiving certolizumab 200 mg became anti-certolizumab antibody positive compared to 2% of patients receiving certolizumab 400 mg. Similarly, in Study 050 8.5% of patients receiving certolizumab 200 mg became anti-certolizumab antibody positive compared to 1.6% of patients receiving the 400 mg dose. Also, while radiographic progression was inhibited in both studies as measured by the change from baseline in modified total Sharp score (mTSS) the degree of inhibition was somewhat greater with the 400 mg dose in Study 050. This modest difference between doses can be seen in the cumulative probability plot for radiographic progression (Figure 1). In this analysis changes from baseline in mTSS are

shown on the y-axis and the cumulative percentage of patients with a particular level of change in mTSS is shown on the x-axis. Higher values of change in mTSS represent greater levels of radiographic progression. As shown in Figure 1 the curves for placebo, 200 mg and 400 mg are similar on the left side of the graph representing patients with little or no radiographic progression. In contrast, the proportion of patients with moderate or large amounts of radiographic progression is markedly lower with certolizumab 400 mg than with placebo as shown on the right side of the figure. The middle curve representing the 200 mg dose is reduced compared to placebo but not quite as much as the 400 mg dose. In contrast, the cumulative probability curve of radiographic progression showed similar inhibition with the 200 mg as with the 400 mg dose in Study 027.



Source: Figure 14.2.5:104

Figure 1: Cumulative Probability Plot of the Change from Baseline in mTSS at Week 24 – Linear Extrapolation – Study 050 (ITT Population) [Sponsor Figure 11:8) page 112 of 6142.]

In summary, there are some differences between the 200 and 400 mg doses that would favor the higher dose, most importantly a somewhat lower level of immunogenicity with the 400 mg dose. Nonetheless overall ACR response rates are similar between the two doses and both doses achieve substantial levels of inhibition of progression of structural damage. In general, the differences between the 200 and 400 mg doses are not large enough to favor the higher dose over the lower one. Taken in their entirety the data suggest that 200 mg q2wk is an appropriate recommended dose.

The proposed dose regimen also contains an initial loading dose of 400 mg SC q2wk x3. The use of this loading dose is supported by the PK modeling that suggests a shorter time to achieving therapeutic blood levels. The better overall results in Studies 027 and 050, which used the loading dose, as compared to 011 and 014, which did not, supports the importance of the loading dose. However, Studies 027 and 050 also differ from the earlier studies in incorporating more frequent q2wk as compared to q4wk dosing.

Finally, the Applicant is proposing an alternative dosing regimen of 400 mg q4wks and proposes that certolizumab may be used as monotherapy or in combination with MTX. As described above, Studies 011 and 014 demonstrated the efficacy of 400 mg q4wk dosing and Study 011 demonstrates efficacy of certolizumab monotherapy. While acknowledging that combination with MTX and q2wk dosing may produce higher efficacy the use of certolizumab as monotherapy and of the alternative 400 mg q4wk dosing regimens appear adequately supported by the data.

6.2.2. Phase 3/ clinical studies essential to regulatory decision

The key studies supporting the efficacy of certolizumab are the Phase 3 trials 027 and 050. Both studies were randomized, double-blind, placebo-controlled, 3-arm trials in patients with active RA despite MTX. Patients in the two certolizumab arms received a loading dose of certolizumab at a dose of 400 mg SC q2wk x3 followed by either 200 mg q2wk or 400 mg q2wk. Both trials contained a primary endpoint of the proportion of patients achieving an ACR20 at 6 months. Study 027 additionally included a second coprimary endpoint assessing radiographic progression using the change from baseline in modified total Sharp score (mTSS). The protocol specified a sequential approach to control for multiplicity by examining the mTSS only if the study had already found statistical significance for the ACR20 coprimary endpoint.

In general, the populations in Studies 027 and 050 were typical of the general RA population. The mean age was approximately 50 years and the mean duration of disease was 6 years. Approximately 80% were female. Patients had moderately to severely active RA with mean tender joint counts of approximately 30 and mean swollen joint counts of approximately 20.

The studies permitted patients to discontinue study mediation early for patients who failed to respond by week 16. Approximately 90% of patients had adequate information to assess the primary endpoint either based on the ACR20 status at 6 months (completers) or based on demonstrated lack of efficacy at week 16 or later (Table 5 from Study 027, similar results were seen in Study 050). Patients with missing data were imputed as non-responders. Discontinuations were more frequent for lack of efficacy in the placebo arms than in the certolizumab arms. Discontinuations due to adverse events were more frequent in the certolizumab arms than in the placebo arms.

Table 5: Patient Disposition: Withdrawals (ITT) – Study 027

Patient Disposition – Study 027 (ITT Population)				
	PBO + MTX	CZP 200 mg q2w+MTX	CZP 400 q2w+MTX	Overall
All patients				1262 (100%)
Screening failures				280 (22%)
Randomized (ITT)	N = 199	N = 393	N = 390	N = 982 (100%)
Safety population	199 (100%)	392 (99.7%)	389 (99.7%)	980 (99.8%) [a]
PP (signs, symptoms)	192 (96%)	370 (94%)	378 (97%)	940 (96%)
PP (structural damage)	191 (96%)	371 (94%)	377 (97%)	939 (96%)
Withdrawn at Week 16	125 (63%)	83 (21%)	68 (17%)	276 (28%)
Completed at Week 16	173 (87%)	355 (90%)	357 (92%)	885 (90%)
Completed at Week 24	45 (23%)	264 (67%)	288 (74%)	597 (61%)
Completed at Week 52	43 (22%)	255 (65%)	274 (70%)	572 (58%)
Total Discontinuations [c]	156 (78%)	138 (35%)	116 (30%)	410 (42%)
Lack of efficacy	141 (71%)	98 (25%)	74 (19%)	313 (32%)
Discontinued due to AEs	3 (2%)	17 (4%)	22 (6%)	42 (4%)
Protocol violations	0	4 (1%)	3 (0.8%)	7 (0.7%)
Patient decision, consent w/dr.	10 (5%)	15 (4%)	11 (3%)	36 (4%)
Lost to follow-up / Unknown	1 (0.5%)	1 (0.3%)	1 (0.3%)	3 (0.3%)
Other [b]	3 (2%)	5 (1%)	6 (2%)	14 (1.4%)
Pts. with non-missing data for the primary efficacy endpoint [d]	93%	90%	89%	90%

(a.) Two patients were randomized but did not receive study drug: Pt.# 118/004 randomized to 200 q2w+MTX withdrew her consent; Pt. #135/005 randomized to 400 q2w+MTX was discontinued due to abnormal ESR/CRP not meeting entry criteria.
(b.) One death (Pt. # 052/002) is reported in the PBO-control treatment group and one death (Pt. # 088/014) is reported in the 400 mg q2w + MTX treatment group. See safety review section for total number of deaths in Study CDP870-027.
(c.) Total discontinuations differ from table #: PBO-Control, 158 vs 156; 200 q2w+MTX, 140 vs 138 ; 400 q2w+MTX, 117 versus 116; Overall 410 vs 415. Abbreviations: PP = per protocol; AEs = adverse events; w/dr.=withdrawn.
(d.) Patients with adequate data who completed or dropped out due to lack of efficacy. Therefore, data is adequate to calculate the primary efficacy analysis for ACR20 responders at Week 52.
Revised from sponsor Table 14.1.1:2,page 261 of 8823.

Certolizumab treatment demonstrated efficacy for signs and symptoms in Study 027 as shown by an increase in the proportion of patient achieving an ACR20 response at 24 weeks, the primary endpoint for the study (

Table 6). A total of 59% and 61% of patients achieved an ACR20 response with the 200 mg and 400 mg doses, respectively, vs. 14% with placebo. Similar results were seen in Study 050 (Table 7). More patients achieved the higher levels of clinical response ACR 50 and ACR 70. The findings on the primary endpoint, the ACR20, were verified by the FDA biostatistical reviewer, Dr. Kate Meaker. Dr. Meaker also confirmed that the statistical analytic plan adequately accounted for multiplicity in view of the two doses tested and the two coprimary endpoints. Sensitivity analyses showed similar results indicating that the positive results were not accounted for by missing data.

The results of secondary endpoints supported the efficacy demonstrated by the primary endpoint. The components of the ACR response criteria all showed improvement with certolizumab, indicating the results on the composite was not driven by one or a subset of the seven individual components. More patients achieved a Major Clinical Response in the certolizumab arms than with placebo as defined by an ACR 70 for 6 consecutive months (13% for the two certolizumab arms vs. 1% for placebo). Examination of subgroup analyses based on baseline demographic features and baseline disease activity revealed no subgroup of patients who did not have a response to certolizumab.

Table 6: Co-Primary ACR20 Response at Week 24 and Week 52 – Study 027

ACR Response - Study 027 (ITT Population)			
	PBO+ MTX N = 199	CZP 200 sc q2w + MTX N = 383	CZP 400 sc q2w + MTX N = 390
ACR-20			
Week 24			
n [c.]	198	388	388
Responder	27 (14%)	288 (59%)	236 (61%)
Odds ratio vs PBP+MTX [a.] (97.5% CI)		9 (5, 16)	10 (6, 17)
p-value		<0.001	<0.001
Week 52			
n [c.]	198	392	388
Responder	26 (13%)	208 (53%)	213 (55%)
Odds ratio vs PBO+MTX (95% CI) [b.]		8 (5, 12)	8 (5, 13)
ACR-50			
Week 24			
Responder	15 (8%)	144 (37%)	155 (40%)
Odds ratio vs PBO+MTX (95%CI) [b.]		8 (4, 13)	9 (5, 15)
p-value		<0.001	<0.001
Week 52			
Responder	15 (8%)	149 (38%)	155 (40%)
Odds ratio vs PBO+MTX (95%CI) [b.]		8 (4, 14)	8 (5, 5)
ACR-70			
Week 24			
Responder	6 (3%)	83 (21%)	80 (21%)
Odds ratio vs PBO+MTX (95%CI) [b.]		9 (3, 22)	8.7 (4, 21)
p-value		<0.001	<0.001
Week 52			
Responder	7 (4%)	83 (21%)	90 (23%)
Odds ratio vs PBO+MTX (95%CI) [b.]		8 (3, 17)	9 (4, 9)
p-value		<0.001	<0.001

Abbreviations: MTX=methotrexate; CI=confidence interval; PBO=placebo.
(a.) Odds ratio: CZP/PBO calculated using logistic regression with factors for treatment and region.
(b.) Wald p-values for the comparison of the treatment groups were calculated using logistic regression with factors for treatment and region.
(c.) n remains the same for calculation of the ACR-50 responses at Week 24 and Week 52, respectively.
Note: patients who withdrew or used rescue medication were considered as non-responders from that time-point forward. Revised from sponsor Table 11:11, page 105 of 8823.

Table 7: ACR-20, -50 and -70 Responses – Study 050

ACR Response - Study 050 (ITT Population) - Study 050			
	PBO + MTX	CZP 200 mg sc q2w + MTX	CZP 400 mg sc q2w + MTX
	N = 127	N = 246	N = 246
ACR-20 at Week 24			
n	127	246	245
Responder	11 (9%)	141 (57%)	141 (58%)
Odds ratio vs PBO + MTX [a.]		14	14
97.5% CI for odds ratio		[7, 31]	[7, 31]
p-value [c.]		<0.001	<0.001
Odds ratio vs CZP 200 mg q2w + MTX [b.]			1
95% CI for odds ratio			[1, 1]
p-value [c.]			1
ACR-50 at Week 24			
Responder	4 (3%)	80 (33%)	81 (33%)
Odds ratio vs PBO + MTX [a.]		17	12
95% CI for odds ratio		[3, 118]	[2, 80]
p-value [c.]		0.004	0.011
Odds ratio vs CZP 200 mg + MTX [b.]			1
95% CI for odds ratio			[1, 2]
p-value [c.]			0.9
Treatment by Region Interaction [d.] p-value = 0.50			
ACR-70 at Week 24			
Responder	1 (0%)	39 (16%)	26 (11%)
Odds ratio vs PBO + MTX [a.]		24	15
95% CI for odds ratio		[3, 176]	[2, 115]
p-value [c.]		0.002	0.008
Odds ratio vs CZP 200 mg + MTX [b.]			0.6
95% CI for odds ratio			[0, 1]
p-value [c.]			0.113
Treatment by Region Interaction [d.] p-value = 0.14			

Study 027 specified inhibition of progression of structural damage as a coprimary endpoint. Patients receiving certolizumab 400 mg and certolizumab 200 mg (0.2 units for both groups) experienced less radiographic progression over 52 weeks than patients receiving placebo (1.3 units) as measured by the change from baseline in the mTSS. The degree of inhibition compared to the placebo group was 92 and 85% with the certolizumab 400 and 200 mg doses, respectively, demonstrating that certolizumab exceeds the level of 75% inhibition that the Division has used to differentiate highly active agents that are described as "inhibiting" from less active agents that are described as "slowing" radiographic progression. Certolizumab reduced both components of the mTSS, namely the erosion component and the joint space narrowing component. Certolizumab treatment also increased the proportion of patients who had no measurable progression of structural damage over one year.

Table 8: Change from Baseline in mTSS at Weeks 24 and Week 52 – Study 027

Comparrison of Change from Baseline in mTSS at 52 Weeks Linear Extrapolation - ITT Population			
	PBO+MTX N = 199	CZP 200 mg sc q2w + MTX N = 393	CZP 400 mg sc q2w + MTX N = 390
Baseline mTSS			
n	199	391	389
Mean (SD)	39 (45)	38 (49)	38 (47)
Change from Baseline at Week 24			
n	180	353	355
Mean (SD)	1.3 (4)	0.2 (3)	0.2 (4)
Difference [a.] vs PBO + MTX (b.)		-0.5	-0.5
95% CI for Difference		[0.8, 0]	[-0.7,0]
p-value [c.]		<0.001	<0.001
% Inhibition vs PBO+MTX [d.]		87%	83%
Change from Baseline at Week 52			
n	181	364	363
Mean (SD)	2.8 (8)	0.4 (6)	0.2 (5)
Difference [a.] vs PBO+MTX [b.]		-0.5	-0.6
97.5% CI for Difference		[-1.5, 0]	[-1.5,0]
p-value [c.]		<0.001	<0.001
% Inhibition vs PBO + MTX [d.]		85%	92%
Difference [a.] vs CZP 200 mg+MTX			0
95% CI for Difference			[0,0]
p-value [c.]			0.89

(a.) The differences are between CZP200/400 mg +MTX minus PBO+MTX.
(b.) Hodges-Lehman point estimate of shift and CI.
(c.) ANCOVA on the ranks with region and treatmetn as factors and rank Baseline as a covariate. Abbreviations: SD=standard deviation; PBO=placebo; MTX=methotrexate; CI=confidence interval. Revised from Table 11:14, page 118 of 8823 and Table 14.2.2:1, page 1360 of 8823.

Studies 027 and 050 assessed improvement in physical function based on the change in the Health Assessment Questionnaire – Disability Index (HAQ-DI). At baseline patients had moderately severe impairment in physical function (1.7 on the 0-3.0 unit scale). Patients treated with certolizumab experienced a greater reduction in HAQ-DI than patients receiving placebo (Table 9). The degree of improvement was 0.6 u, which exceeds the 0.22 u level that has been demonstrated to represent a clinically meaningful change.

Table 9: Health Assessment Questionnaire - Disability Index (HAQ-DI) - Study 027

Comparison of Change from Baseline in HAQ-DI - Study 027 Week 24 and Week 52 - LOCF (ITT Population)			
Visit Treatment	PBO+MTX N = 199	CZP 200 mg sc q2w + MTX N = 393	CZP 400 mg sc q2w + MTX N = 390
Week 24			
Baseline, Mean (SD)	1.7 (1)	1.7 (1)	1.7 (1)
Adj. Mean (SE)[a]	-0.2 (0)	-0.6 (0)	-0.6 (0)
Diff[b] vs PBO+MTX[a]			
Adj. Mean [95%CI][c]		-0.4 [-0.5, -0.3]	-0.4 [-0.5, -0.3]
P-value		<0.001	<0.001
Week 52			
Baseline, Mean (SD)	1.7 (1)	1.7 (1)	1.7 (1)
Adj. Mean (SE)[a]	-0.2 (0)	-0.6 (0)	-0.6 (0)
Diff[b] vs PBO+MTX[a]			
Adj. Mean [95%CI][c]		-0.4 [-0.5, -0.4]	-0.4 [-0.5, -0.4]
P-value		<0.001	<0.001
(a.) ANCOVA with region and treatment as factors and Baseline as covariate. (b.) The differences presented are CZP 200 mg/400 mg + MTX minus PBO+MTX. Abbbreviations: SE=standard error; CI=confidence interval; MTX=methotrexate; PBO=placebo. Revised from sponsor Table 11:16, page 125 of 8823 and Table 14.2.7:43, page 2116 of 8823.			

6.2.3. Other efficacy studies

None

6.2.4. Discussion of primary and secondary reviewers' comments and conclusions

The primary clinical review, Dr. Carolyn Yancey, concluded the studies had demonstrated efficacy of certolizumab for signs and symptoms of RA, for inhibition of progression of structural damage, for improvement in physical function and for inducing a major clinical response. She concluded that certolizumab at a dose of 400 mg q4wks was also efficacious both when given as monotherapy and when given in combination with MTX. The biostatistics reviewer, Dr. Kate Meaker, also concluded that the studies had demonstrated efficacy of certolizumab for both the 200 mg q2wk maintenance dose and the alternative 400 mg q4wk maintenance dose. She concurred that the certolizumab monotherapy trial had demonstrated efficacy.

6.2.5. Pediatric use/PREA waivers/deferrals

Currently there are two approved TNF blockers for treatment of children with polyarticular juvenile idiopathic arthritis (JIA): the soluble TNF receptor fusion protein etanercept (Enbrel) and the anti-TNF monoclonal antibody adalimumab (Humira). The RA guidance document states that efficacy results from adults can be extrapolated to children with the polyarticular form of JIA. Based on the Pediatric Rule, given the rationale for the ability to extrapolate adult efficacy data to children and the previous demonstration that two other products in the class show efficacy in children a case can be made that efficacy studies should not be required for certolizumab. This recommendation is consistent with the recent decision to use extrapolation of adult data to children for Cimzia for Crohn's disease and, therefore, to not require randomized efficacy studies. However, safety and PK studies should be required in children as well

as careful studies of immunogenicity. To further explore whether an efficacy study should be required for polyarticular JIA under PREA we will be raising this issue during an upcoming meeting with PeRC. Based on the prevalence of polyarticular JIA in children of different ages the Applicant should be granted a deferral of studies in the 2-17 year age group and a waiver for the 0-2 year age group.

6.2.6. Discussion of notable efficacy issues

There are no notable efficacy issues.

6.3. Safety

6.3.1. General safety considerations

Currently there are three approved TNF blockers for RA: etanercept (Enbrel), infliximab (Remicade) and adalimumab (Humira). While there are some individual differences between these products in their safety profiles in general terms the safety issues are common to the class. These include infection risk, including reactivation of latent tuberculosis infection and opportunistic infections, risk of malignancy, risk of demyelinating disease and uncommon occurrence of autoimmune disease. While these are serious risks these events are uncommon and the benefits of TNF blockers are believed to outweigh the potential risks. For certolizumab the safety profile was found to be similar to what would be expected for a novel TNF blocker with the major safety signal being tuberculosis.

The safety database of certolizumab in RA was adequate. It exceeded by a large margin the minimum guidelines for products intended for chronic use contained in the ICH E1 guidance document. Overall, the safety database in the RA clinical development program consisted of a total of 2367 patients treated with CZP at the doses recommended for marketing, including 2204 treated for 3 months or longer, 2030 treated for 6 months or longer and 1663 treated for 12 months or longer (Table 10). Patients studied in the certolizumab clinical development program were representative of the general RA population in demographic features and their level of disease activity. Many of the patients in the safety database were receiving the widely used disease modifying anti-rheumatic drug (DMARD) MTX although patients were excluded who were receiving concomitant biologic DMARD's.

Table 10: Extent of Exposure: All Doses in All Studies in RA – Safety Population

Extent of Exposure - All CZP Doses (OL and PBO-Controlled studies) in RA					
	PBO N=647	CZP 200 mg q2w N=640	CZP 400 mg q2w N=1487	CZP 400 mg q4w N=513	All CZP Doses N=2367
Duration of Expos. (days)					
Mean (SD)	127 (73)	226 (117)	357 (162)	794 (514)	497 (324)
Min, Max	14, 366	14, 369	14, 714	28, 1543	14, 1543
Total Exposure (Pt.-Yrs.)	225	396	1453	1116	3,218
Duration of Exposure					
< 3 months	179 (28%)	35 (6%)	61 (4%)	67 (13%)	163 (7%)
≥ 3 to < 6 months	418 (65%)	342 (53%)	124 (8%)	28 (6%)	174 (7%)
≥ 6 to < 12 months	8 (1%)	12 (2%)	577 (39)	65 (13%)	367 (16%)
≥ 12 to < 18 months	42 (7%)	251 (39%)	478 (32%)	46 (9%)	846 (36%)
≥ 18 to < 24 months	0	0	247 (17%)	25 (5%)	535 (23%)
≥ 24 months	0	0	0	282 (55%)	282 (12%)
≥ 12	42 (7%)	251 (39%)	725 (49%)	353 (69%)	1663 (71%)

6.3.2. Safety findings from submitted clinical trials

In the Integrated Summary of Safety, the Applicant reported that 9 of the 1774 certolizumab-treated patients (0.5%) died in the placebo-controlled trials, compared to 1 of 647 placebo-treated patients (0.2%). In the Applicant's analysis 6 of the 9 deaths in the certolizumab group were due to cardiovascular events, none to infections and 1 each to three other categories. Although patients with RA do have an increased risk of death of cardiovascular causes this preponderance of cardiovascular deaths is unusual in RA clinical trials. To investigate the causes of death further the clinical reviewer examined the individual patient narratives and determined that most of the deaths of cardiovascular causes (4 of 6) were actually infectious in nature. Thus the FDA analysis attributes 2 deaths to cardiovascular causes and 5 to infections. This distribution of causes of death is more typical of an immunosuppressive product. However, there remains the question of how the observed mortality rate with certolizumab compares to the expected rate.

To better understand the rate of mortality among certolizumab-treated patients a number of analyses were carried out. First to compare the mortality rate with certolizumab to the rate with placebo it is important to adjust for the longer duration of exposure in the certolizumab group, owing to the early escape provision that was more frequent in the placebo group. As shown in Table 11, when adjusted for the duration of exposure deaths in the certolizumab group occurred at a rate of 0.94/100 pt-yrs compared to 0.44/100 pt-yrs in controls. Given the very small number of events seen in the control group (one event) it is difficult to draw firm conclusions. The mortality rate was next examined in the total RA safety database, including long-term open-label treatment studies. In the total database the rate of death was 0.822/100 pt-yrs. In contrast, the expected rate of death based on mortality rates in the general population is 0.804. These data taken together do not indicate an increased mortality rate in patients treated with certolizumab. Overall, the causes of death in the entire safety database were typical of those expected in an RA population.

Table 11: All Cause Mortality in PBO-Controlled CZP RA Studies

Summary Table - All Cause Mortality CZP Placebo-Controlled RA Clinical Studies Program					
[Studies CZP-002 (iv); CZP-004, -011, -014, -027, -050 (sc); N=1774] **Comparison to Mortality Rates in the Population Exposed to CZP** **1 Death: PBO-Controlled Group ; 9 Deaths: CZP Treatment Groups** Distribution of Cause of Death in Patients Exposed to CZP					
	Number of Observed Cases				
	PBO+ MTX	CZP Doses 200 mg, 400 mg q2w+MTX; 400 mg q4w	Reviewer All CZP Doses	Sponsor All CZP Doses	Expected # of Cases [a]
PBO-Controlled CZP Treatment Group	N=647		N=1774	N=1774	
Cause of Death					
Cardiovascular		2	2	6	10
Infection		5	5	0	1.2
Malignancies		1	1	1	8.4
Injuries (fem frx shock)		1	1	1	2.8
Other non-communicable diseases			0	1	4.6
CZP Treated Patients: TOTAL			9	9	
PBO-Controlled Treatment Group					
Cause of Death					
Cardiovascular	1				
PBO Treated Patients: TOTAL	1				N.A.
OVERALL TOTAL			10	10	
Exposure in Placebo-Controlled Studies					
Total Expo. CZP/ PBO-Contr.	957.4 pt-yrs.				
Deaths per 100pt-yrs.	0.94				
Total Expos. PBO-Contr.	224.9 pt.-yrs.				
Deaths per 100pt-yrs.	0.44				
(a.) The number of deaths is compared to the proportion expected in the general population from the World Health Organization (WHO) Burden of Disease database. The crude rates have been adjusted for age. gender, and region from the 2001 data. Table revised from sponsor Table 3:3, page 11 0f 27, Mortality Report.					

Table 12: Incidence of Mortality in RA Patients Exposed to CZP in PBO-Controlled Studies

Incidence of Mortality in RA Patients Exposed to CZP PBO-Controlled Studies						
	PBO-Controlled Studies					All Pts. in CZP RA Studies
	PBO	CZP 200 q2w+MTX	CZP 400 q2w+MTX	CZP 400 q4w	All CZP Doses (PBO-Cont.)	
Total # Patients	**N = 647**	**N = 640**	**N = 635**	**N = 278**	**N = 1774**	**N = 2367**
Total # Deaths (%)	**1 (0.15%)**	**4 (0.6%)**	**5 (0.78%)**	**0**	**9 (0.5%)**	**25 (1.1%)**
Total Exposure, pt.-yrs.	225	396	410	107	957	3284
Deaths per 100 pt.-yrs.	0.44	1	1.2	0	0.94	0.822
Global Mortality Rate in 100 pt-yrs (CZP RA Studies)						0.822
Weighted Mean Mortality Rate in 100 pt-yrs (General Population)						0.803

A higher rate of serious adverse events was observed among certolizumab-treated patients (11%, 20 per 100 pt-yrs) compared with placebo controls (7%, 18 per 100 pt-yrs) in the randomized trials. Infections were the most important cause of higher serious adverse event rates in the certolizumab group (4% vs. 0.6% with placebo), including tuberculosis, lower respiratory tract infections, bacterial infections and upper respiratory tract infections.

Tuberculosis is a concern with several TNF blockers. The labels for the approved TNF blockers recommend screening and prophylaxis for latent tuberculosis infection before receiving a TNF blocker. A total of 26 cases of tuberculosis were observed in the RA clinical development program for certolizumab (Table 13). None were in the US or North America. The vast majority were among patients from Eastern Europe (23 of 26 cases). During the clinical trials patients were screened with a PPD skin test prior to study enrollment and patients testing positive were treated with anti-tuberculosis drugs before receiving certolizumab. These results suggest that in areas highly endemic for latent tuberculosis infection, such as Eastern Europe, standard procedures for screening and prophylaxis are not adequate to prevent cases of tuberculosis.

Table 13: Cases of Tuberculosis in All CZP Clinical Development Programs

Number of TB Cases by Region and Indication (as of July 2007)				
	Crohn's Disease	Rheumatoid Arthritis	Psoriasis	Total
# Unique Patients	2,508	2,367	117	5,118
Total exposure (pt.[a]-yrs.)	2286.3 (2287.9[a])	3997.6 (4000.5[a])	97 (97[a])	6404.8 (6409.3[a])
North America	0	0	0	0
Western Europe	1	2	1 *	4
Eastern Europe	0	23 **	0	23
Japan	1	0	0	1
South Africa ***	5	0	0	5
Rest of the World	1	1 *	0	2
Total	8	26	1	35 (14 *)

Sponsor Table 9:1 and 9:2, page 14 and 13 of 62, Risk of TB with CZP Global Health Outcomes Research.
a. Total exposure for confirmed cases only Expsoure by Region.
* Confirmed cases.
** 12 of 23 cases from Eastern Europe were confirmed cases.
*** South Africa is shown as a separate region in this table yet is part of the Rest of the World for all other tables.

In addition to the serious infections the overall rate of infections was higher in the certolizumab group (38% vs. 23%, unadjusted for differing durations of exposure). In general, the types of infections were typical of those seen in the general RA population.

Malignancies are a concern with certolizumab because of its immunosuppressive mechanism of action and data for other TNF blockers suggesting a possible increased rate in certain patient populations. Overall the rate of malignancies was not increased in certolizumab-treated patients compared to the expected rate. A total of three lymphoma cases were observed with a standardized incidence ratio (SIR) of 4.97 [95% CI: 1.03 to 14.54]. Given that the rate of lymphoma is increased in RA patients compared to the general population and that the risk of lymphoma is particularly increased in patients with highly active disease a higher rate of lymphoma is not unexpected. An SIR of 4.97 is

within the range that has been observed previously in patients receiving other TNF blockers.

Exploration of common adverse events, discontinuations due to adverse events or laboratory abnormalities did not reveal additional safety signals.

One aspect of laboratory evaluations calls for additional comment. Patients treated with other TNF blockers have developed autoantibodies (antinuclear antibodies (ANA's) and anti-dsDNA antibodies) more frequently in clinical trials than controls. The rate of conversion to autoantibody positivity varies depending on the specific product. The majority of patients developing autoantibody positivity have no clinical adverse outcomes; however, clinical autoimmunity has developed in a small number. In their analysis of the autoantibody data the Applicant contends that only a very small number of patients convert to autoantibody positivity. However, the data submitted do not support this conclusion. With the assays for ANA and anti-dsDNA used in the Phase 3 studies 027 and 050 the majority of patients were positive at baseline. This is highly unusual in this patient population and suggests there was a problem with the assay.

In summary, the major safety concern observed with certolizumab treatment was an increased risk of serious infections, in particular tuberculosis.

6.3.3. Safety update

The results of the safety update are included in the discussion above.

6.3.4. Immunogenicity

Antibodies to certolizumab developed in some treated patients (Table 14). Overall the rate of immunogenicity was lowest in patients receiving the highest dose tested, namely 2% in the certolizumab 400 mg q2wk plus MTX group. The rate was higher in patients receiving the dose proposed for approval, namely 10% in the certolizumab 200 mg q2wk group. The rate of immunogenicity was also higher in patients receiving certolizumab monotherapy, namely 22%. Efficacy was diminished in patients developing anti-certolizumab antibodies.

Table 14: Anti-CZP Antibody Positive Patients in CZP RA Studies

Anti-CZP Antibody Positive Patients - Study 011, 014, 027 and 050 in RA					
	CZP 200 mg [a.] sc q2w + MTX N = 640	CZP 400 mg sc q2w + MTX N = 633	CZP 400 mg sc q4w + MTX N = 124	CZP 400 mg sc N = 111	All CZP Doses N = 1508
Antibody Positive	63 (10%)	12 (2%)	5 (4%)	25 (22.5%)	105 (7%)

6.3.5. Discussion of primary reviewer's comments and conclusions

The primary reviewer identified serious infections, in particular tuberculosis, as the major safety concern with certolizumab. Overall, Dr. Yancey concluded that the safety profile

of certolizumab was similar to that observed with other TNF blockers and similar to what is currently in the Cimzia label.

6.3.6. Discussion of notable safety issues

Overall the major safety concern with certolizumab is uncommon but serious infections. In general, the safety profile is similar to what is observed with the other approved TNF blockers.

An additional safety issue arose during the review of the submission by DMEP in OSE. DMEP was concerned about the fact that if the current submission is approved that there would be a lyophilized product available for Crohn's disease and a liquid product available in prefilled syringes for patients with RA. DMEP was concerned that if a patients with RA got a package with the lyophilized formulation that they would not know how to administer it. A teleconference was held with the Applicant to discuss this issue and a proposal for resolution was discussed. The proposal involves the inclusion of instructions for administration to accompany each kit. (b) (4) DMEP agreed that this plan would address their concerns.

7. Advisory Committee Meeting

Since the safety and efficacy data for certolizumab appear similar to what has been observed with other products in this class no advisory committee was deemed necessary.

8. Financial Disclosure

No potentially conflicting financial interests were identified.

9. Labeling

9.1. Physician labeling

At the time of completion of this CDTL memo, detailed consideration of the label was just beginning. The label should contain sufficient information on response rates with certolizumab monotherapy and with q4wk dosing that prescribers can see that although these regimens provide efficacy the efficacy is not as high as with the q2wk dosing and with use in combination with MTX. The rate of immunogenicity with different dose regimens should also be included. Finally, the description of autoantibody formation should be modified compared to that proposed by the Applicant because of the very high background rate of autoantibody positivity.

10. DSI audits

DSI inspected study sites in Slovakia and in Russia. At the time of writing of this memo the final DSI review had not been completed. However, an e-mail from DSI dated 8/21/08 indicated that the inspection report from the Slovakian site was acceptable and that the inspection of the Russian site appeared acceptable as well.

11. Conclusions and recommendations

11.1. Regulatory action

Data from four adequate and controlled trials support the efficacy of certolizumab in patients with rheumatoid arthritis. Two trials studied the efficacy of the proposed dose regimen consisting of an initial loading dose of 400 mg SC q2wks x3 followed by certolizumab 200 mg q2wks in combination with MTX. These trials showed ACR20 response rates at 6 months of approximately 60% compared to placebo response rates of 14%. The studies also showed inhibition of progression of structural damage over 12 months with rates of progression reduced by approximately 85% compared to placebo controls. Patients treated with certolizumab also experienced greater improvement in physical function than controls and more frequently achieved Major Clinical Responses. Certolizumab was demonstrated effective when used with MTX and when used as monotherapy. While the 200 mg q2wks dose regimen showed higher response rates the 400 mg q4wk dose regimen was also efficacious.

The safety profile of certolizumab is similar to that of other TNF blocking agents. The main safety concern is serious infection.

There remains one unresolved issue, namely the amount of [redacted] (b) (4) that may be present in the product. So long as the [redacted] (b) (4) issue can be resolved in an acceptable manner, certolizumab should be approved for the treatment of moderately to severely active rheumatoid arthritis.

11.2. Safety concerns to be followed postmarketing

The major safety concerns that should be followed postmarketing are those known to be associated with immunosuppressive agents in RA, including serious infections, autoimmune diseases, malignancies and demyelinating events.

11.3. Risk Evaluation and Mitigation Strategy (REMS)

11.3.1. General considerations on the need for, and goals of, any REMS beyond standard labeling and pharmacovigilance

Cimzia currently has a Medication Guide and a REMS. The REMS is in the process of being modified because of the recent identification of a class issue involving all TNF blockers, namely the occurrence of cases of histoplasmosis that is not promptly recognized by clinicians. The REMS is to be modified to communicate concerns

regarding histoplasmosis to clinicians and to monitor whether physicians are becoming more aware of the possibility of histoplasmosis in patients at risk.

11.4. Postmarketing studies

11.4.1. Required studies

Generally, when the Agency has approved new immunosuppressive products for RA the action has been associated with postmarketing commitments/requirements to carry out long-term, open-label treatment trials in approximately 1000-1500 patients for 5 years to explore long-term safety. The Agency has also expected applicants to study the effects of the product on the ability to mount responses to therapeutic vaccination. The Agency has not mandated registry studies in adult RA. However, registries of all the approved biologics have been set up in Europe (UK, Sweden, Germany and other countries) and in the US (Dr. Fred Wolfe's National Data Bank for Rheumatic Diseases (NDB) and the Consortium of Rheumatology Researchers of North America (CORRONA)). Although these registries have not generated new safety signals data from the registries have been very useful in further characterizing safety signals that were identified through other means (e.g., spontaneous adverse event reports).

One important issue to consider for certolizumab is whether to require long-term open-label treatment studies of safety and whether to require a registry. Currently a great deal of information is available on the safety profile of TNF blockers with long-term use. The data on safety of TNF blockers is derived from long-term open-label treatment studies of the approved TNF blockers and from registries both in the US and in Europe. Five-year data are available on patients treated with etanercept and with adalimumab and studies are ongoing out to 10 years. As the fourth TNF blocker to be approved for RA it is unclear what additional information would be derived from long-term open-label treatment studies or from additional registries studies with certolizumab. It is the recommendation of this reviewer and of the primary reviewer that adequate data are available on long-term use of TNF blockers and that the Applicant should not be required to conduct additional long-term treatment studies or registries in adult patients with RA. Discussions are planned with OSE to determine whether long-term treatment studies or registries should be required of the Applicant.

11.4.2. Commitments (PMCs)

No additional PMC's are necessary.

11.4.3. Other agreements with Sponsor

None.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

MEDICAL REVIEW(S)

Clinical Review -- Addendum

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation 2
Division of Anesthesia, Analgesia and Rheumatology Products

Addendum to Medical Officer Review

Date: May 6, 2009

To: File, BLA 125271/0

From: Jane L. Gilbert, M.D., Ph.D. 5/7/09
ODE2 - Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Re: Need for additional studies of blood pressure effects of Cimzia
CIMZIA® (certolizumab pegol)
UCB, Inc.
Proposed indication: Rheumatoid arthritis

The purpose of this addendum is to address the consultation from the Division of Cardiovascular and Renal Products (Cardiorenal consult) which was requested to address the complete response from UCB and which was received after my review was finalized. More specifically, it is to further discuss the nature of post-marketing requirements that are recommended.

In my original review, I argued that "even in the absence of additional risk factors such as prior hypertension Cimzia appears to be associated, independently, with hypertensive adverse events." I recommended labeling changes specifically to identify this fact as well as to underscore that a baseline history of hypertension and the use of concomitant NSAIDS and/or corticosteroids could exacerbate the likelihood of a hypertensive adverse event.

I further argued that:

> *In addition to the labeling changes there should be a post-marketing requirement to establish a mechanism to study and monitor potentially serious cardiovascular events such as those discussed in this review.*

The recommendation for a post-marketing requirement (PMR) was expressed in general terms. However, in light of the Cardiorenal consult, additional discussion may be useful. Specifically, the Cardiorenal consult states:

> *We disagree with the sponsor's conclusion that "there is no apparent clinically relevant risk for HTN associated with CZP use." There is a possible risk that is poorly characterized. Most helpful would be a careful study of BP changes throughout the interdosing interval and with long term follow-up. Whether and when to require such a study is your decision.*

While I agree with the conclusion that there is a poorly characterized risk for hypertension, a PMR for a well-designed clinical registry may be sufficient to characterize this risk. It is possible, for example, to design a clinical registry which, in addition to identifying cardiovascular and other adverse events, also:

1. includes people with a baseline history of hypertension and/or other cardiovascular comorbidities, as well as people without a baseline history

2. measures blood pressure at baseline and at prescribed intervals between doses, and

3. tabulates the initiation of new or increased doses of anti-hypertensive medications.

If a clinical study registry such as this is feasible, then it may be adequate to more precisely characterize the risk of hypertension. If such a registry cannot be designed, then a PMR to design and implement a clinical study to measure blood pressure would be appropriate. Such a study need not be a cardiovascular outcome study.

CLINICAL REVIEW

Application Type	BLA 125271
Letter Date	March 13, 2009
Stamp Date	March 13, 2009
PDUFA Goal Date	May 13, 2009
Reviewer Name	Jane L. Gilbert, M.D., Ph.D.
Review Completion Date	May 1, 2009
Through	Jeffrey Siegel, M.D. Clinical Team Leader
Established Name	Certilizumab pegol
(Proposed) Trade Name	CIMZIA®
Therapeutic Class	TNF inhibitor
Applicant	UCB, Inc.
Priority Designation	Class I Resubmission
Formulation	200 mg liquid (1mL) per vial in a prefilled single-use syringe
Dosing Regimen	400 mg sc at 0, 2 and 4 weeks, followed by 200 mg sc every other week
Indication	Rheumatoid Arthritis
Intended Population	Active RA unresponsive to MTX

Jane L. Gilbert 5/1/09

Jeffrey N. Siegel 5/1/09

MAY - 1 2009

TABLE of CONTENTS

I. Introduction

Certolizumab Pegol (Cimzia, CZP) is a pegylated, genetically-engineered, humanized monoclonal antibody Fab' fragment derived from a murine hybridoma, with specificity for tumor necrosis factor-alpha (TNF-α, TNF). It is under review for the indication of Rheumatoid Arthritis (RA). It was approved April 22, 2008 for the treatment of Crohn's disease (BLA 125160); BLA 125271 for the treatment of rheumatoid arthritis was submitted December 6, 2007. The FDA issued a Complete Response (CR) on January 2, 2009 due to a concern about a potential cardiovascular safety signal based upon a higher proportion of cardiovascular deaths in subjects receiving CZP.

Subsequent to issuance of the CR, the review division, DAARP, obtained a Cardio-Renal consult. The consult did not identify a "signal for a difference in CV deaths or all cause mortality." Yet, the consultant raised several other questions related to cardiovascular safety.

Based upon the concerns identified in the Cardio-Renal consult, the Agency requested that the Sponsor respond to five questions. These questions addressed the following categories of events: congestive heart failure, tachyarrhythmias, stroke/transient ischemic attack, hypertension, and thrombotic events.

UCB submitted a complete response to the CR on March 12, 2009. The complete response consists of a re-analysis of the pooled database from six placebo-controlled studies, including: C87002, C87004, C87011, C87014, C87027 and C87050. The CZP and placebo (PBO) dose groups included:

- CZP 200 mg every 2 weeks (q2w) (following 3 loading doses of 400mg each, 2 weeks apart) (N=640)
- CZP 400 mg sc every 2 weeks (q2w) (N=635)
- CZP 400 mg sc every 4 weeks (q4w) (N=278)
- All CZP Doses (includes subjects which received doses other than the 3 regimens bulleted above, primarily in the phase 2 studies, C87002 and C87004) (N=1774)
- Placebo (N=647)

The CR uses the following groupings of MedDRA preferred terms:

- Heart Failure/Cardiomyopathy: Ischaemic cardiomyopathy, **Cardiomyopathy,** Congestive cardiomyopathy, Cardiac failure, Cardiac failure chronic
- Tachyarrhythmia/tachycardia : Tachycardia, Tachyarrhythmia, Tachycardia paroxysmal, Sinus tachycardia, Atrial flutter, Atrial fibrillation, Atrial tachycardia,
- Stroke/transient ischemic attack (TIA): Cerebrovascular accident, **Cerebral infarction,**

Cerebral ischaemia, Ischaemic cerebral infarction, Transient ischaemic attack

- Hypertension: Hypertension, Essential hypertension, Systolic hypertension, Hypertensive crisis, Procedural hypertension
- Venous thrombosis/phlebitis: Phlebitis, Phlebitis superficial, Thrombophlebitis, Deep vein thrombosis, **Thrombophlebitis superficial**, Venous thrombosis limb, Venous thrombosis, **Pulmonary embolism**, Vena cava thrombosis

The terms which are bolded were added as medically relevant but not on the FDA-provided list of preferred terms.

The re-analysis is directed towards answering the five questions posed by the Agency. To accomplish this task, the Sponsor identified subjects with treatment-emergent adverse events (TEAEs) defined by each of the preferred terms; each subject underwent further review to identify medical history, concomitant medications and additional TEAEs.

The Complete Response Safety Update (CR SU) provides safety data from three additional clinical studies (C87015, C87028 and C87051).

Section II of this review will focus upon the Cardio-Renal consult that was completed in January 2009. Section III of this review will analyze the data presented in the CR for each of the five questions that the Sponsor was asked to address. Section IV will summarize the major points of the review.

The manner and conduct of the studies used to support the original BLA were deemed satisfactory in the review during the first cycle. Therefore, these will not be re-assessed at this time. Rather, this review will focus upon the re-analysis of data and the adequacy of this re-analysis.

II. Cardio-Renal Consult

A consult from the Division of Cardiovascular and Renal Products was completed on January 27, 2009. This consult was in response to the review division's concern about a possible cardiovascular (CV) safety signal with (CZP). Specifically, five of nine deaths in the Cimzia arm, compared to one in placebo, were reported as CV in nature. The consultant was asked to review the data and "provide an assessment about the possible CV safety signal and ... recommendations regarding what additional information would be needed to evaluate further the CV safety of Cimzia."

The Cardio-Renal consult reviewed data from four placebo-controlled phase 3 studies: C87011, C87014, C87027, C87050. These included 552 patients in the placebo arm and 1,510 patients treated with three different doses of CZP. Viewed by person exposure years (PEYs), there were 220 PEYs for placebo and 953 PEYs for subjects receiving CZP. (Note that the CR from the Sponsor included two additional studies: 87002 and 87004.)

The Cardio-Renal consult concludes that "there is not a strong signal for a difference in CV deaths or all cause mortality."

Since, however, CV deaths "do not typically occur in isolation but are usually accompanied by non-fatal CV events" the consultant further examines other CV event rates. These are provided in Table 1 below.

Table 1: CV Events in the Placebo-Controlled Periods of the Phase 3 Cimzia Trials in RA

	patients with events		rate/1000 patients		rate/1000 PEYs	
event	placebo	Cimzia	placebo	Cimzia	placebo	Cimzia
any ischemic heart disease	3	14	5.4	9.3	13.6	14.7
myocardial infarction	1	5	1.8	3.3	4.5	5.2
heart failure/cardiomyopathy	0	4	0.0	2.6	0.0	4.2
cardiac tachyarrhythmia	4	24	7.2	15.9	18.2	25.2
atrial fibrillation	1	8	1.8	5.3	4.5	8.4
hypertension	9	82	16.3	54.3	40.9	86.0
stroke/tia	1	9	1.8	6.0	4.5	9.4
stroke	1	5	1.8	3.3	4.5	5.2
tia	0	4	0.0	2.6	0.0	4.2
venous thrombosis/phlebitis	0	20	0.0	13.2	0.0	21.0

Source: Cardio-Renal consult: Table 4. PEYs represent person exposure years.

The following comments, related to this table were provided in the consult:

1. As with CV deaths, rates that look bad by patient do not appear differentiated by PEY. The rates per PEY for any ischemic heart disease (including MI, angina, and general reports of ischemic or coronary hear disease) are not differentiated between Cimzia and placebo.

2. There are few cases, but the available ones suggest a possible effect of Cimzia on heart failure. Such an effect is not inconsistent with the possible effects of other TNF blockers and, because of the low numbers, adds little to what is known about activities of TNF blockers in heart failure.

3. We have included in "cardiac tachyarrhythmia" AE reports of tachycardia, so this event definition does not imply a serious arrhythmia. Of greater interest is the increased rate of atrial fibrillation. Note that two of the deaths were accompanied by atrial fibrillation. Atrial fibrillation is associated with increased risks of stroke and heart failure. While the stroke rates are not clearly differentiated between placebo and Cimzia, the combined stroke/TIA rates are. Stroke, of course, is strongly associated with hypertension (discussed next). Finally, if there is some direct cardiotoxic effect of TNF blockade responsible for worsening heart failure, we would not be surprised to have atrial fibrillation as part of the clinical picture.

4. Clearly there are more hypertensive AEs reported for Cimzia than for placebo. . . . What is less clear is what these hypertensive AEs represent, i.e., timing relative to agent administration, severity, duration, etc. Three of the AEs, all in Cimzia groups, were reported as serious. We are aware of, but have not sumarized here, the sponsor's analyses that BP measurements done in the trials do not show increased mean or high outlier values-see our conclusions below.

Based upon the analysis and comments provided in the Cardio-Renal consult, the review division, DAARP, posed five questions for the Sponsor to address in the CR. The next section of this review will assess the Sponsor's response to these questions.

III. Analysis of Complete Response to Questions

The first question posed by the FDA concerned heart failure and cardiomyopathy:

Question 1: Congestive Heart Failure/Cardiomyopathy.

In the placebo-controlled portions of the CZP trials there were 4 patients with heart failure/cardiomyopathy in the CZP group and none in the control group. Submit analysis of the risk of heart failure/cardiomyopathy in the controlled portions of the CZP trials. If your analysis indicate that the data are not fully described in you proposed product label submit any appropriate changes to the label. In addition, to further explore the potential risk of heart failure/cardiomyopathy with CZP we recommend you consider incorporating measurement of B type natriuretic peptide (BNP) and possibly troponin in future clinical trials.

Table 2 below displays data provided by the Sponsor describing the incidence of heart failure and cardiomyopathy in the placebo-controlled studies for rheumatoid arthritis. The Sponsor identifies, here, an incidence of 0.3 per hundred patients in individual arms as well as overall. This corresponds closely to the incidence identified in the obtained Cardio-Renal consult where the analysis showed a rate of 2.6 per 1000 patients (approximately, 0.3%) for heart failure/cardiomyopathy.

Table 2: Incidence of heart failure/cardiomyopathy TEAEs in placebo-controlled rheumatoid arthritis studies

Preferred term	PBO (N=647)		CZP 200mg sc q2w (N=640)		CZP 400mg sc q2w (N=635)		CZP 400mg sc q4w (N=278)		All CZP Doses (N=1774)	
	n (%)	100 pt-yrs	n (%)	100 pt-yrs	n (%)	100 pt-yrs	n (%)	100 pt-yrs	n (%)	100 pt-yrs
Number of heart failure/ cardiomyopathy AEs	0	0	2 (2, 0.3)	0.49	2 (2, 0.3)	0.47	0	0	5 (5, 0.3)	0.50
Cardiac failure	0	0	1 (1, 0.2)	0.24	0	0	0	0	2 (2, 0.1)	0.20
Cardiac failure chronic	0	0	0	0	1 (1, 0.2)	0.24	0	0	1 (1, 0.1)	0.10
Congestive cardiomyopathy	0	0	0	0	1 (1, 0.2)	0.24	0	0	1 (1, 0.1)	0.10
Ischaemic cardiomyopathy	0	0	0	0	1 (1, 0.2)	0.24	0	0	1 (1, 0.1)	0.10

AE=adverse event; CZP=certolizumab pegol; N=number in population; n=number with adverse event; pt-yrs=patient-years; q2w=every 2 weeks; q4w=every 4 weeks; sc=subcutaneous; TEAE=treatment-emergent adverse event.

Source: Table 1:1, Complete Response.

An additional source of information about cardiovascular events is the Complete Response Safety Update which includes data from 10 studies with a cutoff date of June 30, 2008. Based upon 2367 subjects who received Cimzia for 4909 years of exposure, 16 individuals, or 0.7% were classified as having "heart failure NEC."

The analyses described above identify a few patients (0.3 – 0.7%) in various Cimzia-treated arms that experience adverse events involving heart failure or cardiomyopathy. No such patients are identified in the placebo arm. This suggests a possible higher risk of heart failure/cardiomyopathy in Cimzia-treated patients.

The risk of worsening heart failure is consistent with possible effects of other TNF blockers. The Sponsor plans to include the following language in the label:

5.3 Heart Failure
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including CIMZIA. CIMZIA has not been formally studied in patients with CHF; however, in clinical studies in patients with CHF with another TNF blocker, worsening congestive heart failure (CHF) and increased mortality due to CHF were observed. Exercise caution in patients with heart failure and monitor them carefully [see *Adverse Reactions (6.1)]*.

The analysis and labeling provided in the CR is adequate to address this question. However, post-marketing requirements should include efforts to monitor the incidence of congestive heart failure to make certain that this does not develop more frequently than anticipated. Such efforts would probably be best accomplished with establishment of a registry.

Question 2. Tachyarrhythmia/Tachycardia

In the placebo-controlled portions of the CZP trials, there were 24 AE reports of tachyarrhythmias/tachycardia among CZP treated patients and 4 reports in controls. Of particular concern is the higher proportion of CZP-treated patients with atrial fibrillation (8 [in] the CZP group; 1 in controls). We also note that two of the deaths in CZP-treated patients was accompanied by atrial fibrillation. Atrial fibrillation is associated with increased risks of stroke and heart failure. Submit analysis of the risk of tachyarrhythmia/tachycardia and atrial fibrillation in the controlled portions of the CZP trials. If your analysis indicate[s] that the data are not fully described in your proposed label submit appropriate changes to the label.

The table below displays data provided by the Sponsor summarizing the incidence of tachyarrhythmias/tachycardia in the placebo-controlled studies for rheumatoid arthritis.

Table 3: Incidence of tachyarrhythmias/tachycardia TEAEs in placebo-controlled rheumatoid arthritis studies

Preferred term	PBO (N=647)		CZP 200mg sc q2w (N=640)		CZP 400mg sc q2w (N=635)		CZP 400mg sc q4w (N=278)		All CZP Doses (N=1774)	
	n (%)	100 pt-yrs	n (%)	100 pt-yrs	n (%)	100 pt-yrs	n (%)	100 pt-yrs	n (%)	100 pt-yrs
Number of tachyarrhythmia/ tachycardia AEs	4 (4, 0.6)	1.63	13 (11, 1.7)	2.70	8 (8, 1.3)	1.90	2 (2, 0.7)	1.75	25 (23, 1.3)	2.32
Tachycardia	0	0	6 (6, 0.9)	1.47	3 (3, 0.5)	0.71	1 (1, 0.4)	0.87	10 (10, 0.6)	1.00
Atrial fibrillation	1 (1, 0.2)	0.41	3 (3, 0.5)	0.73	2 (2, 0.3)	0.47	1 (1, 0.4)	0.87	7 (7, 0.4)	0.70
Arrhythmia	1 (1, 0.2)	0.41	0	0	1 (1, 0.2)	0.24	0	0	2 (2, 0.1)	0.20
Sinus tachycardia	2 (2, 0.3)	0.82	2 (2, 0.3)	0.49	0	0	0	0	2 (2, 0.1)	0.20
Atrial flutter	0	0	1 (1, 0.2)	0.24	0	0	0	0	1 (1, 0.1)	0.10
Atrial tachycardia	0	0	1 (1, 0.2)	0.24	0	0	0	0	1 (1, 0.1)	0.10
Tachyarrhythmia	0	0	0	0	1 (1, 0.2)	0.24	0	0	1 (1, 0.1)	0.10
Tachycardia paroxysmal	0	0	0	0	1 (1, 0.2)	0.24	0	0	1 (1, 0.1)	0.10

AE=adverse event; CZP=certolizumab pegol; N=number in population; n=number with adverse event; PBO=placebo; pt-yrs=patient-years; q2w=every 2 weeks; q4w=every 4 weeks; sc=subcutaneous; TEAE=treatment-emergent adverse events.

Source: Table 1.3 , Complete Response

Comparing the events identified in the placebo group with those summarized in the final column which tabulates events for *all* Cimzia doses[1] one notes an incidence of tachyarrhythmia of 1.3% for Cimzia-treated subjects compared with 0.6% for placebo-

[1] It is appropriate to analyze the data for all doses in aggregate since no dose response is noted.

treated patients. The Cardio-Renal consult identified comparable percentages of 1.6% (Cimzia-treated) and 0.7% (placebo). Therefore, for the comprehensive category of tachyarrhythmia the data analyzed by both the Sponsor and the Cardio-Renal consultant identify an incidence that is about twice as high in Cimzia-treated patients as in placebo-treated patients. However, as noted in the Cardio-Renal consult, tachyarrhythmia includes tachycardia and does not, therefore, necessarily represent a serious arrhythmia.

In contrast, the narrower category of "atrial fibrillation," which was associated with two of the deaths in the development program, may represent a more serious arrhythmia. For this category of events, the Sponsor identifies an incidence of 0.4% among the Cimzia-treated patients compared with 0.2% among placebo-treated patients. The comparable percentages identified in the Cardio-Renal consult are 0.5% (Cimzia) vs. 0.2% (placebo). Therefore, for the narrow category of atrial fibrillation, both the Sponsor and the FDA Cardio-Renal consultant identify a risk that is small, in approximately the same range and twice as great with Cimzia as placebo. As noted by the Cardio-Renal consultant, the risk of atrial fibrillation is potentially concerning as it may be associated with an increased risk of stroke and heart failure; though stroke does not occur at a higher rate among Cimzia-treated patients, heart failure does and atrial fibrillation may be part of this picture.

The Sponsor acknowledges that there was a higher incidence of tachyarrhythmia and atrial fibrillation in active treatment groups and recommends that the label be changed to include atrial fibrillation as well as arrhythmia in Section 6.1 (Other Adverse Reactions). The proposed label would read:

> *Cardiac disorders: Angina pectoris, arrhythmias, atrial fibrillation, cardiac failure, hypertensive heart disease, myocardial infarction, myocardial ischemia, pericardial effusion, and pericarditis.*

The analysis of tachyarrhythmias is adequate to address this question. The recommended label modification is acceptable. In addition, the Agency should seek a post-marketing requirement to establish a registry that would track the frequency of cardiac tachyarrhythmias including atrial fibrillation.

Question 3: Stroke/TIA

In the placebo controlled portions of the CZP trials there were 8 AE reports of stroke/transient ischemic attack (TIA) among CZP-treated patients and 1 in controls. Submit analyses of the risk of stroke/TIA AEs in the controlled portions of the CZP trials. If your analyses indicate that the data are not fully described in your proposed product label submit appropriate changes to the label.

Table 4 below displays data from the Sponsor describing treatment–emergent adverse events identified as stroke or TIA.

Table 4: Summary of stroke/TIA TEAEs in placebo-controlled rheumatoid arthritis studies

Preferred term	PBO (N=647)		CZP 200mg sc q2w (N=640)		CZP 400mg sc q2w (N=635)		CZP 400mg sc q4w (N=278)		All CZP Doses (N=1774)	
	n (%)	100 pt-yrs	n (%)	100 pt-yrs	n (%)	100 pt-yrs	n (%)	100 pt-yrs	n (%)	100 pt-yrs
Number of CVA/TIA AEs	1 (1, 0.2)	0.41	3 (3, 0.5)	0.73	5 (4, 0.6)	0.95	1 (1, 0.4)	0.87	9 (8, 0.5)	0.80
TIA	0	0	2 (2, 0.3)	0.49	2 (2, 0.3)	0.47	0	0	4 (4, 0.2)	0.40
CVA	1 (1, 0.2)	0.41	1 (1, 0.2)	0.24	3 (2, 0.3)	0.47	0	0	4 (3, 0.2)	0.30
Ischaemic cerebral infarction	0	0	0	0	0	0	1 (1, 0.4)	0.87	1 (1, 0.1)	0.10

AE=adverse event; CVA=cerebrovascular accident; CZP=certolizumab pegol; N=number in population; n=number with adverse event; pt-yrs=patient-years; PBO=placebo; q2w=every 2 weeks; q4w=every 4 weeks; sc=subcutaneous; TEAE=treatment-emergent adverse events; TIA=transient ischemic attack.

Source: Table 1.5, Complete Response

Review of this table reveals that the incidence of combined TIA/CVA is about twice as great for Cimzia-treated patients as for those receiving placebo (0.5% vs. 0.2%). Furthermore, most of this increase is attributable to TIA (0.2% vs. 0). This pattern is consistent with the analysis provided in the Cardio-Renal consult (Table 1) which identifies stroke/TIA in approximately 0.6% of Cimzia-treated patients compared with 0.2% of those receiving placebo. Similar to the Sponsor's results, the analysis provided in the Cardio-Renal consult identifies the fact that most of the increase in the incidence of these events is attributable to TIA rather than stroke: (0.3% vs 0 for TIA; 0.3 % vs. 0.2% for stroke).

Though the number of events is small, the incidence of stroke and TIA appears to be approximately twice as great in Cimzia-treated patients compared with those on placebo. Despite this fact, which is evident in data provided by both the Sponsor and the Cardio-Renal consult, these events are not identified in the proposed label as potential adverse events.

The analysis is adequate to address this question. However, no labeling changes are proposed. In light of the analysis, labeling changes reflecting a possible increased risk for the combined events of stroke/TIA and TIA alone should be incorporated in the label. The Agency should, additionally, require (as a post-marketing-requirement) the establishment of a registry to track the incidence of strokes and TIAs in patients receiving Cimzia.

Question 4: Hypertensive events

In the placebo-controlled portions of the CZP trials, there were 82 reports of tachyarrhythmias among CZP-treated patients and 9 reports in controls. Three of these AEs were as serious, all among CZP-treated patients. We are aware of your analyses of blood pressure measurements during the trials that did not show an increase in blood pressure in the CZP group compared to controls. However if the timing of the adverse events relative to the administration of CZP was different from the timing of blood pressure measurements, it is not clear whether the timing of blood pressure measurements was adequate to capture elevations in blood pressure that may have contributed to the hypertensive AE. One particular concern is that CZP may raise blood pressure in the period following administration but that blood pressure falls back to baseline by the time of the next dose. Submit analyses of the risk of hypertensive adverse events in the controlled portions of the CZP trials that include the timing of these events in relation to the last dose of study medication. Include an analysis of the severity and duration of these hypertensive events and the impact of concomitant medications. The analyses should also consider whether the timing of study-mandated blood pressure measurements in relation to the administration of CZP was adequate to assess elevation occurring in the period soon after administration of CZP or if the measurements were carried out late after administration just prior to the subsequent dose. If your analyses indicate that the data are not fully described in your proposed product label, submit appropriate changes to the label.

This request involves analysis of four aspects related to the AE of hypertension:

(a) timing relative to the last dose of Cimzia
(b) severity
(c) duration, and,
(d) the impact of concomitant medication.

Table 5 below displays data from the original BLA submission. It provides the mean change in systolic and diastolic blood pressure from baseline to the last study visit. It demonstrates small decreases in virtually all groups regardless of study arm or prior history of hyptertension.

Table 5: Summary of end mean change in systolic and diastolic blood pressure by baseline diagnosis of hypertension in placebo-controlled rheumatoid arthritis studies C87004, C87011, C87014, C87027 and C87050

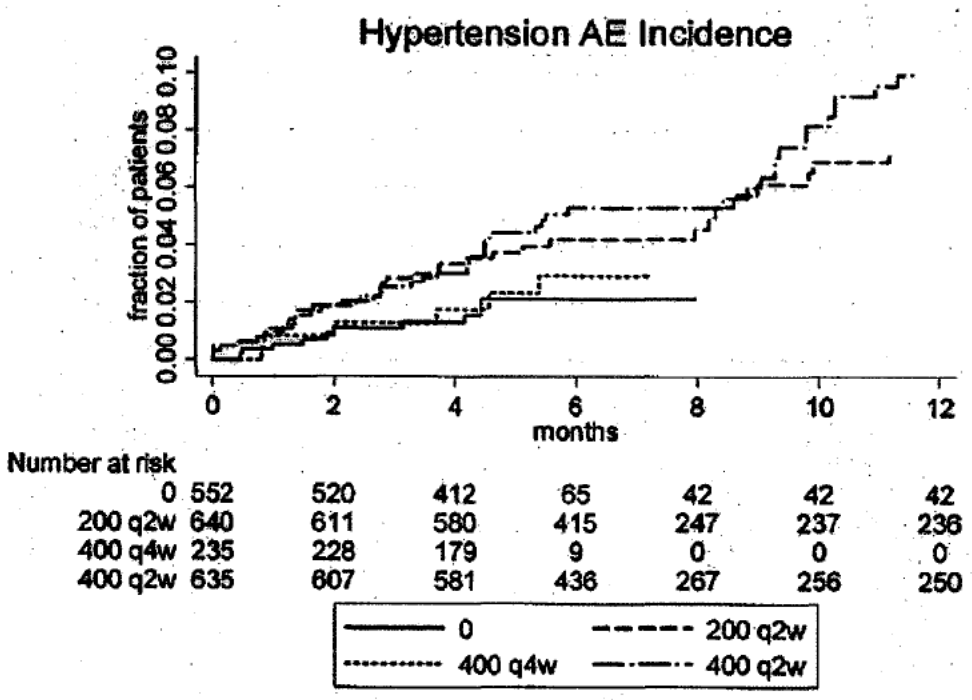
	PBO (N=635)	CZP 200mg sc q2w (N=640)	CZP 400mg sc q2w (N=635)	CZP 400mg sc q4w (N=278)	All CZP Doses (N=1750)
Systolic					
All subjects mean change (SD)	n=619 -1.7 (15.03)	n=638 -2.4 (14.09)	n=632 -1.4 (14.43)	n=277 -2.2 (15.48)	n=1738 -2.0 (14.46)
BL HTN=Yes	n=197/202 -2.8 (16.96)	n=214/216 -4.1 (15.77)	n=216/217 -2.6 (15.97)	n=81/81 -5.1 (19.09)	n=553/556 -3.6 (16.63)
BL HTN=No	n=422/433 -1.1 (14.03)	n=424/424 -1.6 (13.10)	n=416/418 -0.8 (13.54)	n=196/197 -1.0 (13.59)	n=1185/1194 -1.2 (13.27)
Diastolic					
All subjects mean change (SD)	n=619 -0.4 (9.4)	n=638 -1.4 (9.13)	n=632 -0.8 (9.84)	n=277 -0.4 (9.46)	n=1738 -0.9 (9.58)
BL HTN=Yes	n=197/202 -1.2 (10.7)	n=214/216 -2.7 (9.67)	n=216/217 -1.7 (10.25)	n=81/81 -2.0 (10.05)	n=553/556 -1.9 (10.44)
BL HTN=No	n=422/433 -0.0 (8.7)	n=424/424 -0.7 (8.78)	n=416/418 -0.3 (9.60)	n=196/197 0.3 (9.15)	n=1185/1194 -0.4 (9.12)

BL=baseline; CZP=certolizumab pegol; HTN=hypertension; N=number in population; PBO=placebo; q2w=every 2 weeks; q4w=every 4 weeks; SD=standard deviation.

Data sources: Supplemental Table 18 and Supplemental Table 19 from the original BLA 125271

However, Table 1, taken from the Cardio-Renal consult, provides evidence of a higher rate of hypertensive adverse events with Cimzia than placebo: 5.4% of Cimzia-treated patients developed hypertension compared with 1.6% of those receiving placebo. Figure 1 below further demonstrates the relationship between CZP, PBO and hypertensive AEs.

Figure 1: Hypertension AEs by Dosing Group in the Phase 3 Cimzia Trials in Rheumatoid Arthritis



Source: Cardio-Renal consult, Figure 3.

(a) Timing

The table below (Table 6) responds to the first issue raised in the question: timing. It addresses whether the timing of BP measurement (at the end of the study period) could result in missed AEs such as those occurring prior to or after the end of the study period. The table contains data on pre and post-dose measurements of blood pressure. Pre-dose measurements were obtained 15 minutes before each injection; post-dose measurements were obtained 30 minutes after each injection.

Table 6: Incidence of pre dose and post dose SBP≥140 mmHG and/or DBP≥90 mmHG on ≥ 2 post—baseline visits analyzed in placebo-controlled rheumatoid arthritis studies C87004, C87011, C87014, C87027 and C87050

Timing of BP measurement	PBO N=635	CZP 200 mg q 2w N=640	CZP 400 mg q 2w N=635	CZP 400 mg q 4w N =278	All CZP N = 1750
pre-dose	265/605	258/637	267/627	124/274	702/1721
	44%	41%	43%	45%	41%
post-dose	245/593	254/637	241/626	115/273	654/1708
	41%	40%	39%	42%	38%
Source Table 1:9 Complete Response					

Table 6 demonstrates that the percentage of subjects who had hypertension after the dose of Cimzia was not higher than the percentage with hypertension before. Furthermore there is no study arm where the percent with hypertension increases after the medication is dosed.

To explore the importance of the timing of blood pressure measurement, further analysis was undertaken to assess the incidence of hypertension in relationship to the day of dosing. Table 7 below displays the data from that analysis; it does not reveal a consistent relationship between the day of receiving Cimzia and the development of the TEAE of hypertension.

Table 7: Summary of reported incidence of TEAEs of hypertension in relation to previous dose of study medication in placebo-controlled rheumatoid arthritis studies

Timing of TEAE of HTN in relation to dose	PBO (N=647)		CZP 200mg sc q2w (N=640)		CZP 400mg sc q2w (N=635)		CZP 400mg sc q4w (N=278)		All CZP Doses (N=1774)	
	No. AEs (n, %)	IR	No. AEs (n, %)	IR	No. AEs (n, %)	IR	No. AEs (n, %)	IR	No. AEs (n, %)	IR
All subjects	N=647		N=640		N=635		N=278		N=1774	
Day of Dosing	3 (3, 0.5)	856.05	12 (11, 1.7)	409.56	13 (12, 1.9)	119.95	2 (2, 0.7)	27.06	30 (28, 1.6)	134.28
Days 1 to 4 post dose	2 (2, 0.3)	695.71	5 (4, 0.6)	168.71	9 (8, 1.3)	93.09	1 (1, 0.4)	59.96	15 (13, 0.7)	103.70
Days 5 to 9 post dose	0	0	7 (6, 0.9)	217.63	13 (13, 2.0)	140.52	0	0	22 (21, 1.2)	150.90
Days 10 to 14 post dose	2 (2, 0.3)	333.56	19 (19, 3.0)	292.45	17 (16, 2.5)	67.88	0	0	38 (37, 2.1)	116.93
≥15 days post dose	3 (3, 0.5)	615.59	1 (1, 0.2)	112.73	1 (1, 0.2)	27.16	6 (4, 1.4)	89.69	11 (9, 0.5)	93.81

Source: Complete response, Table 1:11.

In Table 7, five time periods are identified: day of dosing, days 1 to 4 post dose, and so on. Comparing the results for the 674 patients in the PBO arm with those for patients in all CZP doses (N=1774), one notes that in each category, except for the category ≥15 days post dose, the incidence of TEAEs of hypertension is greater in the CZP arms. (That is, 1.6> 0.5, 0.7>0.3, 1.2> 0, 2.1>0.3. In the over 15 days post dose category the percentage of subjects experiencing a TEAE is the same in both placebo and CZP arms.) Among CZP treated subjects, however, there does not appear to be a consistent, monotonically increasing relationship between hypertension and the time since dose of the drug. This suggests that the timing of the blood pressure measurement in relationship to administration of CZP was unlikely to have resulted in inaccuracies or missed identification of TEAEs.

(b) Severity

Table 8 provides information about the severity of hypertensive adverse events and the relationship to baseline hypertension. Only a small number of events were categorized as severe. Furhtermore, while there does not appear to be a trend towards more serious adverse events in the CZP arm compared to PBO, the data in the table do show that, for each category, there are more hypertensive AEs in CZP than comparable PBO arms. For example, among all subjects with baseline hypertension receiving CZP, 9% experienced an AE compared with only 2% among those receiving PBO; among all those receiving CZP without a history of baseline hypertension, 3% experienced mild AEs whereas only 1% of those receiving PBO experienced an AE. The pattern holds throughout: comparing similar categories that differ only by whether or not the subjects were on CZP or PBO reveals that hypertensive AEs in the CZP arm exceed those in the PBO arm. Although the rates of hypertensive AEs are higher in the group with baseline hypertension, higher rates of hypertensive AEs are seen in the Cimzia groups both in patients with a baseline history of hypertension and without .

Table 8: Incidence of hypertension by severity and baseline hypertension

Study Drug	Baseline HTN	AE Severity	TEAEs
CZP (N=1774)	Yes (N= 565)	All	50 (9%)
		mild	27 (5%)
		moderate	23 (4%)
		severe	2 (<1%)
	No (N=1209)	All	46(4%)
		mild	32 (3%)
		moderate	13 (1%)
		severe	1 (<1%)
	All	All	116 (96)/ 5%
PBO (N=647)	Yes (N = 206)	All	4 (2%)
		mild	3 (1%)
		moderate	1 (<1%)
		severe	0
	No (N = 441)	All	6 (1%)
		mild	4 (1%)
		moderate	2 (<1%)
		severe	0.00%
	All	All	10 (10)/1.5%

Source:Response to Questions, Table 1:12

(c) Duration

Table 9 provides information about the duration of hypertensive AEs and how this is related to both baseline history of hypertension as well as use of CZP or PBO. Though there are more AEs in CZP-treated subjects compared with PBO, these do not appear to be disproportionately of long duration. Consistent with the preceding analysis, the data in Table 9 further identify the association between baseline hypertension and the development of hypertensive AEs in Cimzia-treated patients.

Table 9: Duration of TEAEs of hypertension by baseline history of hypertension in placebo-controlled rheumatoid arthritis studies: number of subjects (percent)

		Duration of TEAE (days)					
Drug	History of hypertension	0-1	2-14	15-30	31-90	91 to <ongoing	ongoing/not reported
CZP	Y (N = 565)	10 (2%)	18 (3%)	4 (1%)	9 (2%)	4 (1%)	14 (2%)
	N (N = 1209)	4 (<1%)	6 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)	33 (3%)
aPBO	Y (N = 206)	2 (1%)	0	1 (<1%)	1 (<1%)	0	0
	N (N = 441)	1 (<1%)	0	2 (<1%)	1 (<1%)	0	2 (<1%)

Source: Complete Response, Table 1:13.

(d) Concomitant medications

Table 10 presents data demonstrating the relationship between TEAEs of hypertension, study drug, and, concomitant use of NSAIDs or corticosteroids (CS). It appears that use of concomitant medications in itself does not affect the incidence of hypertension; among those subjects receiving CZP, a higher percent of AEs is seen among those who did not use a concomitant medication (e.g. of those who received either an NSAID or CS, 5% developed an AE of hypertension compared with 7% of those who did not receive a concomitant medication). For subjects receiving placebo there was a slightly higher incidence of hypertension among those also receiving a concomitant medication. However, it is notable that a comparison between the CZP and PBO group within each and every category reveals that there is a higher incidence of a hypertensive AE among the CZP subjects compared with PBO. These data therefore suggest that AEs of hypertension were *not* due to the use of concomitant medications.

Table 11 further clarifies the relationship between concomitant medication and hypertensive AEs by dividing all categories by presence or absence of a baseline history of hypertension. Consider, first, the association with baseline hypertension alone (fourth column). One sees that prior history appears to predispose a patient to a hypertensive AE: 9% with a baseline history vs. 4% without a baseline history (in the CZP arm) experienced an AE. In the PBO arm, the impact of prior history seems less important: 2% vs. 1% experienced AEs, with and without the baseline history, respectively.

One should also note, however, that regardless of whether or not there was a prior history of hypertension, there was a higher incidence of AEs of hypertension in the CZP arm compared with PBO: 9% vs 2% for those with a prior history of hypertension and 4% vs 1% for those without a prior history.

The data further demonstrate that, among those receiving CZP and who *also* have a history of hypertension, there are more TEAEs of hypertension *when using concomitant medication* compared with those who do not have history of hypertension; that is, for those with a prior history of hypertension, 8% of those taking NSAID or CS experienced

an AE whereas less than 1% experienced an AE without concomitant medication. For subjects without a history of hypertension, the difference in incidence of a hypertensive AE is 3% vs <1% for those taking either NSAID or CS. *This suggests that, should CZP be approved, patients with a history of hypertension who are to receive CZP should be advised to use concomitant medication cautiously.*

For patients receiving PBO, concomitant use of NSAID or CS has the expected result and is associated with a small increase in the percent of hypertensive events among those with a prior history of hypertension: 2% vs 0 %. For subjects without the prior history there is little difference in the incidence of a hypertensive AE among those who did or did not take a concomitant medication.

Finally, one should note that in each and every category, the incidence of AEs of hypertension is greater in the CZP arm (the top half of the table) compared to the PBO arm. This suggests that the association between Cimzia and hypertensive AEs is independent of both prior history *and* concomitant medication.

In summary, the higher rate of hypertensive adverse events identified initially in the Cardio-Renal consult raised the question of whether Cimzia has the effect of raising blood pressure or whether the apparently higher rate was due to idiosyncracies of timing. Since the original data described blood pressure measurements obtained just before the next dose, this did not exclude the possibility that blood pressure could be elevated in the time period immediately after receipt of CZP. Data describing blood pressure measurements submitted in this response do not provide evidence for an elevation of blood pressure in the immediate period after CZP is given. Further, as discussed above, though a baseline history of hypertension as well as concomitant use of medications such as NSAIDs or corticosteroids may be associated with the development of hypertensive AEs, the impact of CZP seems to exist independently of these additional factors.

The data provided in the CR is adequate to assess the association between Cimzia and hypertensive AEs.

Table 10: Incidence of TEAEs of hypertension in relation toNSAID and Corticosteroid (CS) use in placebo controlled rheumatoid arthritis studies

Study Drug	Baseline HTN	AE Severity	TEAEs	NSAID USE		CS USE		N or CS USE	
				Y	N	Y	N	Y	N
N				1442	332	1040	734	1652	122
CZP (N = 1774)									
	All	All	116 (96)	78(71)	38(25)	65(55)	51(41)	103(88)	13(8)
			5%	5%	7.50%	5%	6%	5%	7%
				N-yes	N-no	C-yes	C-no	N/C yes	N/C no
				521	126	379	268	590	57
PBO (N= 647)									
	All	All	10(10)	9 (9)	1 (1)	6(6)	2(2)	4(4)	0
			1.50%	2%	1%	2%	1%	1%	0

Source: Complete Response, Table 1:12 with additional information from Response to Questions

Table 11: Incidence of TEAEs of hypertension and their severity inrelation to NSAID and Corticosteroid (CS) use and baseline hypertension in placebo-controlled rheumatoid arthritis studies*

Incidence of TEAEs of hypertension and their severity in relation to CS and NSAID use and baseline hypertension in placebo controlled rheumatoid arthritis studies. *									
Study Drug	**Baseline HTN**	**AE Severity**	**TEAEs**	**NSAID USE**		**CS USE**		**N or CS USE**	
				Y	N	Y	N	Y	N
N				1442**	332	1040	734	1652	122
CZP (N=1774)	**Yes** N= 565	All	50 (9%)	34 (6%)	16 (3%)	29 (5%)	21 (4%)	48 (8%)	2(<1%)
	No N=1209	All	46(4%)	37 (3%)	9 (1%)	26 (2%)	20 (2%)	40 (3%)	6(<1%)
	All	All	116 (96)	78 (71)	38 (25)	65 (55)	51 (41)	103 (88)	13 (8)
			5%	5%	7.50%	5%	6%	5%	7%
				N-yes	N-no	C-yes	C-no	N/C yes	N/C no
				521	126	379	268	590	57
PBO (N=647)	**Yes** N = 206	All	4 (2%)	4 (2%)	0	2 (1%)	2 (1%)	4 (2%)	0 (0%)
	No N= 441	All	6 (1%)	5 (1%)	1	4(1%)	2	5 (1%)	1 (<1%)
	All	All	10 (10)	9 (9)	1 (1)	6 (6)	2 (2)	4 (4)	0
			1.50%	2%	1%	2%	1%	1%	0

**Complete Response,Table 1:12 with additional information from Response to Questions.*

** where not noted, the number in a cell represents the number of persons who experienced an event....where there are two numbers, the one outside of parentheses represents number of events, the one inside parentheses represents number of persons.

(e) Label

The following table provides the information given in the label regarding the AE of hypertension.

(b) (4)

Though the label includes hypertension as an adverse reaction experienced by more than 3% of the population, additional attention should be given to the use of NSAIDs and corticosteroids for patients receiving Cimzia who also have a baseline history of hyptertension. The Sponsor should propose language which highlights the risk of a hypertensive AE in subjects with a baseline history of hypertension who also receive concomitant NSAIDs or corticosteroids. In addition, the post- marketing requirement should include a mechanism to gather data describing hypertensive AEs.

Question 5: Venous thrombosis/phlebitis

In the placebo-controlled portions of the CZP trials, there were 20 AE reports of venous thrombosis/phlebitis among CZP-treated patients and 1 in controls. Submit analyses of the risk of venous thrombosis/phlebitis AEs in the controlled portions of the CZP trials. If your analyses indicate that the data are not fully described in your proposed product label submit appropriate changes to the label.

The Cardio-Renal consult (Table 1) identified a higher rate of venous thrombosis/phlebitis in Cimzia-treated patients (1%) compared with those receiving placebo. Table 13 from the Complete Response provides additional data from the Sponsor on this category of adverse events.

Table 13: Summary of venous thrombosis/phlebitis TEAEs in placebo-controlled rheumatoid arthritis studies

Preferred term	PBO (N=647)		CZP 200mg sc q2w (N=640)		CZP 400mg sc q2w (N=635)		CZP 400mg sc q4w (N=278)		All CZP Doses (N=1774)	
	n (%)	100 pt-yrs	n (%)	100 pt-yrs	n (%)	100 pt-yrs	n (%)	100 pt-yrs	n (%)	100 pt-yrs
Number of venous thrombosis/ phlebitis AEs	1 (1, 0.2)	0.41	9 (8, 1.3)	1.96	15 (11, 1.7)	2.63	2 (2, 0.7)	1.74	28 (23, 1.3)	2.32
Phlebitis	0	0	5 (5, 0.8)	1.22	5 (5, 0.8)	1.18	0	0	10 (10, 0.6)	1.00
Deep vein thrombosis	0	0	2 (1, 0.2)	0.24	1 (1, 0.2)	0.24	1 (1, 0.4)	0.87	5 (4, 0.2)	0.40
Thrombophlebitis	0	0	0	0	4 (4, 0.6)	0.95	0		4 (4, 0.2)	0.40
Venous thrombosis	0	0	0	0	2 (1, 0.2)	0.24	1 (1, 0.4)	0.87	3 (2, 0.1)	0.20
Venous thrombosis limb	0	0	0	0	1 (1, 0.2)	0.24	0	0	2 (2, 0.1)	0.20
Phlebitis superficial	0	0	1 (1, 0.2)	0.24	0	0	0	0	1 (1, 0.1)	0.10
Pulmonary embolism	1 (1, 0.2)	0.41	0	0	1 (1, 0.2)	0.24	0	0	1 (1, 0.1)	0.10
Thrombophlebitis superficial	0	0	1 (1, 0.2)	0.24	0	0	0	0	1 (1, 0.1)	0.10
Vena cava thrombosis	0	0	0	0	1 (1, 0.2)	0.24	0	0	1 (1, 0.1)	0.10

AE=adverse event; CZP=certolizumab pegol; N=number in population; n=number with adverse events; PBO=placebo; pt-yrs=patient-years; q2w=every 2 weeks; q4w=every 4 weeks; sc=subcutaneous; TEAE=treatment-emergent adverse event.

Source: Complete Response, Table 1:14

As presented in this table, there does appear to be an increased incidence of venous thrombosis/phlebitis in Cimzia-treated patients compared with those receiving placebo. The proportion involved is higher than that identified in the original Cardio-Renal consult: approximately 2% compared to 1%. However, approximately half of the events identified here are related to phlebitis compared to more serious events such as DVT, thrombophlebitis, or pulmonary embolism.

To reflect identification of this risk, the sponsor proposes changing the label to include thrombophlebitis in Section 6.1: "Other Adverse Reactions" under "vascular disorders."

The analysis of thrombosis/phlebitis provided in the Complete Response is adequate to address the issue. Consistent with the analysis previously undertaken in the FDA Cardio-Renal consult, it demonstrates a small increase in events in patients receiving drug compared to placebo. The proposed labeling changes are adequate.

IV. Summary and Conclusions

This section will summarize the analysis provided above for each question.

Question 1 addresses heart failure and cardiomyopathy. The analysis provided in the CR is consistent with prior FDA analyses. It demonstrates a small increased risk of worsening heart failure (0.3-0.7% among Cimzia-treated patients). The identified risk is consistent with possible effects of other TNF blockers. The language that the Sponsor plans to include in the label is adequate to address this risk.

Question 2 addresses tachyarrhythmia/tachycardia. The data and anlysis provided in the CR is consistent with prior FDA analyses. It demonstrates a low risk of tachyarrhythmia and atrial fibrillation in patients receiving Cimzia compared to placebo. Though the risk is low (<1%) it, nevertheless, is twice that seen in placebo. The Sponsor recommends modifying the label to include information in the section pertaining to "Other Adverse Reactions." The proposed language is adequate to address this risk.

Question 3 addresses adverse events related to stroke/TIA. Though only a small number of events are involved, the incidence of stroke and TIA appears to be twice as great in Cimzia-treated patients as in those receiving placebo. The label does not include information about the risk of stroke/TIA. The labeling should be revised to reflect the risk of stroke/TIA.

Question 4 addresses the risk of hypertensive adverse events. In a number of the tables presented in the section devoted to hypertension, the incidence of hypertensive adverse events is greater in Cimzia-treated than placebo-treated patients. The risk of a hypertensive adverse event in Cimzia- treated patients is exacerbated when there is a baseline history of hypertension and when concomitant NSAIDs or corticosteroids are used. The data suggest that Cimzia should be used cautiously in those with a baseline history of hypertension. The data further suggest that patients with a history of hypertension who are to receive Cimzia should be monitored carefully if they are to receive concomitant NSAIDs or corticosteroids. It should, however, be emphasized, that even in the absence of additional risk factors such as prior hypertension Cimzia appears to be associated, independently, with hypertensive adverse events. The Sponsor should propose labeling changes to reflect the need for caution when using Cimzia in (1) patients with a baseline history of hypertension and (2) patients who are to receive concomitant NSAIDs or corticosteroids.

Question 5 addresses the risk of venous thrombosis/phlebitis. The data provided in the CR are consistent with analyses previously undertaken at FDA and demonstrate a small increase in events in patients receiving drug compared to placebo. The Sponsor proposes

labeling changes to include thrombophlebitis in the section of the label that describes "Other Adverse Reactions." These proposed changes are adequate.

In addition to the labeling changes there should be a post-marketing requirement to establish a mechanism to study and monitor potentially serious cardiovascular events such as those discussed in this review.

The applicant's response to the Complete Response adequately addresses the issues raised. The BLA should be approved with revisions to the proposed package insert.

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 29, 2009

From: Thomas A. Marciniak, M.D.
Medical Team Leader
Division of Cardiovascular and Renal Products (HFD-110)

Subject: Cimzia (BLA 125271) cardiovascular safety complete response

Through: Norman Stockbridge, M.D., Ph.D. 4/29/09
Division Director

To: Kathleen Davies, R.P.M.
Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

This memo responds to your consult to us dated April 17, 2009, regarding the sponsor's responses to our questions about cardiovascular (CV) safety signals with cetolizumab pegol (Cimzia, CZP) for rheumatoid arthritis (RA). In a previous consult response we noted that there were some CV safety signals in the Cimzia trials database and you drafted five questions to the sponsor. We comment on the sponsor's responses to the five questions below.

1. Risk of heart failure/cardiomyopathy

The sponsor's findings are similar to ours that there a few cases of heart failure or cardiomyopathy in the Cimzia arms and none with placebo. We agree with the sponsor's conclusion that the risk of heart failure is covered adequately by the current warning in the proposed label.

2. Risk of tachyarrhythmia/tachycardia

The sponsor also notes slightly higher rates of tachyarrhythmias and atrial fibrillation in the Cimzia groups than with placebo. We agree with the sponsor that adding atrial fibrillation to the label is adequate to express this risk.

3. Risk of stroke/transient ischemic attacks

The sponsor's findings regarding strokes and TIAs are identical to ours. The sponsor concludes that, because the differences are slight and RA patients are predisposed to such events, the

proposed label does not need to be changed. The rates of strokes, expressed per PEY, are not different for the Cimzia and placebo groups. There is a small difference in the TIA rates because there were none in the placebo group. Because this signal is weak, we agree that a description in the label is not absolutely mandatory.

4. Risk of hypertensive adverse events

The sponsor's new contrived analyses of BP changes are not very helpful in understanding possible effects of Cimzia upon BP. The major new table regarding incidence of pre- (15 minutes before) and post-dose (30 minutes after) SBP≥140 and/or DBP≥90 on 2 or more post-baseline visits during the first 8 post baseline measurements appears contrived or selected to generate negative results. BP is a continuous variable yet, for these pre-dose vs. post-dose measurements, the sponsor only presents a strangely crafted categorical analysis. We believe that it would be much more helpful to present mean post-dose changes from the pre-dose values on the same day. Furthermore, it is not clear that 30 minutes post-dose is the only appropriate time for monitoring BP changes. Measurements throughout the interdosing interval (2-4 weeks) are needed.

The other analyses (the mean BP changes from baseline to last visit, the timing of the hypertensive AEs related to dosing, and the analyses of baseline hypertension, severity of AEs, and concomitant medication use) are helpful in excluding a large, sustained effect upon BP. That most hypertensive AEs were reported at 10-14 days (with drug given every 14 days) probably reflects the detection of the AE at the visit rather than any pharmacologic timing.

Including hypertensive event rates in the AE table in the label is a necessity. We disagree with the sponsor's conclusion that "there is no apparent clinically relevant risk for HTN associated with CZP use." There is a possible risk that is poorly characterized. Most helpful would be a careful study of BP changes throughout the interdosing interval and with long term follow-up. Whether and when to require such a study is your decision.

5. Risk of venous thrombosis/phlebitis

The sponsor concludes that, during the CZP studies, the active treatment group was noted to have a higher incidence of thromboembolic events and proposes to add it to the label in an "Other Adverse Reactions" section. This addition is reasonable.

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 27, 2009

From: Thomas A. Marciniak, M.D.
Medical Team Leader
Division of Cardiovascular and Renal Products (HFD-110)

Subject: Cimzia (BLA 125271) cardiovascular safety

Through: Norman Stockbridge, M.D., Ph.D.
Division Director

To: Kathleen Davies, R.P.M.
Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

This memo responds to your consult to us dated January 6, 2009, regarding a possible cardiovascular (CV) safety signal with cetolizumab pegol (Cimzia, CZP) for rheumatoid arthritis (RA). As you note in your consult request, you are particularly concerned about five of nine deaths in the Cimzia arm compared to one in the placebo arm reported as CV in nature. The attribution of causes of death is confounded by the comorbidities of serious infections expected from this immunosuppressive agent. You have asked us to review these data and provide our assessment about the possible CV safety signal and our recommendations regarding what additional information would be needed to evaluate further the CV safety of Cimzia. We address your request below in detail.

Before giving our evaluation we do note that Cimzia shares with other TNF blockers a warning regarding worsening of heart failure and new onset of heart failure. While TNF blockers have consistently failed in trials aimed at treating heart failure, the epidemiological evidence is less clear whether TNF blocker use in RA is associated with worsening heart failure. Furthermore, we are unaware of a study documenting the mechanism for the failure of TNF blockers in treating HF. We have tried to address HF events in the Cimzia trials.

We certainly agree that the deaths in the Cimzia trials in RA were confounded by multiple factors, including sepsis. We show our summary of the most relevant features of the deaths in Table 1.

Table 1: Deaths during the Placebo-Controlled Periods of Cimzia Phase 3 Trials in RA

age/sex	days from start	days from last drug	death cause	CV*	comment
64F	33	20	hepatic neoplasm	no	varices, elevated LFTs at baseline
73F	259	147	cirrhosis	no	died nursing home MI on palliative care
63F	104	5	sudden	yes	severe dyspnea, sudden death at home - placebo
83F	16	1	stroke	yes	stroke with subarachnoid hemorrhage, meningoencephalitis
58M	150	52	sudden	yes	empyema, sudden death, myocardial necrosis on autopsy
75F	240	2	sudden	yes	preceding afib, PVC, ischemia on ECG, died home no autopsy
67M	125	13	sudden	yes	"fell" and pronounced DOA
78F	63	48	sudden	yes	headaches, ?borreliosis, sick sinus, cardiomyopathy, arrested, no autopsy
63F	193	53	MI	yes	preceding afib, stroke; cardiac enzyme elevated and ant'r MI by ECG
65F	70	13	shock	no	femur fracture, "cardiac shock"

* whether a cardiovascular event was the principle cause or a major contributor to death

We assess that in seven of the deaths (6 Cimzia, 1 placebo) a CV event was the principle cause or a major contributor to death. These events include one stroke, one well-documented myocardial infarction (MI), and five sudden deaths or arrests that are typically associated with MIs, arrhythmias, or pulmonary embolisms. We agree with other reviewers that alternative explanations for several of these deaths are possible, e.g., meningoencephalitis, empyema. However, as an initial estimate of whether Cimzia presents any CV risk, we used the seven potentially CV-related deaths.

The double-blind, placebo-controlled experience with Cimzia in RA includes seven trials: two single dose pharmacology studies, a phase 2 dose-ranging study of three administrations at 4 week intervals, and four phase 3 studies of longer durations with every 2 or 4 week dosing. The single dose pharmacology studies are useful only for appraising severe, acute toxicity and the phase 2 study has a limited duration of exposure and an adverse event pattern that appears different than the phase 3 studies. Hence we consider the most appropriate exposures to consider are during the placebo-controlled periods of the phase 3 trials. The latter exposures are complicated by multiple drug arms in some studies and varying durations of treatment by arm due to protocol rules regarding discontinuations for lack of efficacy. We summarize the numbers of patients in the placebo-controlled periods of the phase 3 trials in Table 2 and our calculations of the exposures in Table 3.

Table 2: Numbers of Patients in the Phase 3 Cimzia Trials in RA

study	weeks	placebo	200 q2w	400 q4w	400 q2w	all Cimzia
011	24	109	0	111	0	111
014	24	119	0	124	0	124
027	52	199	392	0	389	781
050	24	125	248	0	246	494
total		552	640	235	635	1,510

Table 3: Person Exposure Years (PEYs) in the Placebo-Controlled Periods of the Phase 3 Cimzia Trials in RA

study	placebo	200 q2w	400 q4w	400 q2w	all Cimzia
011	33		45		45
014	46		52		52
027	97	311		324	635
050	44	110		111	221
total	220	421	97	435	953

We calculated PEYs by calculating the days between the first and last administration of Cimzia for each patient in the initial, double-blind, placebo-controlled phase of each trial, adding 28 days for continuing exposure to Cimzia after the injection, and dividing by 365.25. Our results are similar to, but not identical to, the sponsor's; the slight differences in PEYs do not affect any interpretations of rates. Note that the exposures are about 2.7:1 Cimzia:placebo by patient counts and 4.3:1 by PEYs.

Using the above exposures the CV death rates are 1.8 per thousand placebo and 4.0 per thousand Cimzia patients, for a relative risk of about 2.2. However, using the PEY exposures the corresponding rates are 4.5 and 4.0 per thousand PEYs, for a relative risk of 0.9. If alternative estimates of CV deaths are used, i.e., attributing one or two more Cimzia deaths to infection, the difference in the mortality rate per patient would be smaller and per PEY would favor Cimzia.

So, depending upon which of the preceding analyses one trusts more, there is a suggestion of an increased risk of CV death for Cimzia or possibly a protective effect. Kaplan-Meier incidence plots of deaths, similar to the PEY analyses, also do not suggest a significant effect upon short-term mortality. We show the incidence plots by dosing group in Figure 1 and by all Cimzia combined vs. placebo in Figure 2. There is not a strong signal for a difference in CV deaths or all cause mortality.

Figure 1: Death Incidence by Dosing Group in the Phase 3 Cimzia Trials in RA

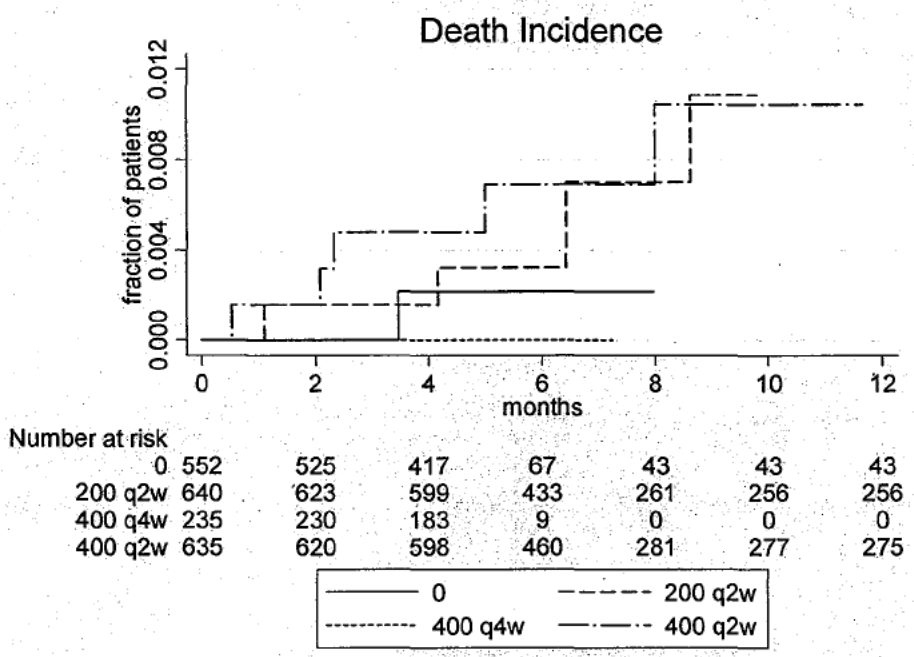
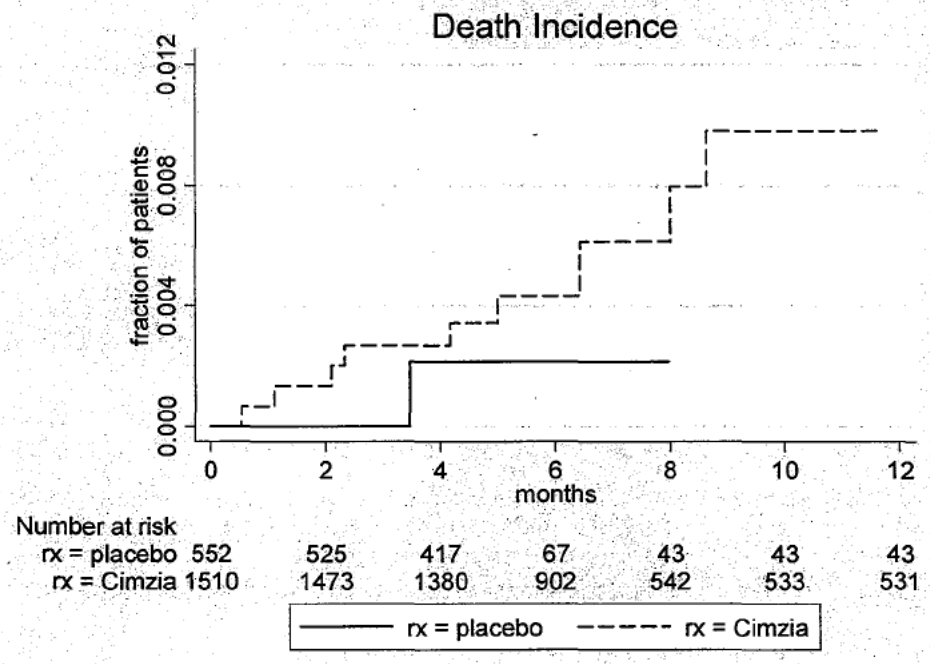


Figure 2: Death Incidence by All Cimzia vs. Placebo in the Phase 3 Cimzia Trials in RA



p = 0.46 by log rank test

CV deaths do not typically occur in isolation but are usually accompanied by non-fatal CV events. Hence we examine the CV event rates next. We show in Table 4 selected CV event rates in the placebo-controlled periods of the Phase 3 Cimzia trials in RA.

Table 4: CV Events in the Placebo-Controlled Periods of the Phase 3 Cimzia Trials in RA

	patients with events		rate/1000 patients		rate/1000 PEYs	
event	placebo	Cimzia	placebo	Cimzia	placebo	Cimzia
any ischemic heart disease	3	14	5.4	9.3	13.6	14.7
myocardial infarction	1	5	1.8	3.3	4.5	5.2
heart failure/cardiomyopathy	0	4	0.0	2.6	0.0	4.2
cardiac tachyarrhythmia	4	24	7.2	15.9	18.2	25.2
atrial fibrillation	1	8	1.8	5.3	4.5	8.4
hypertension	9	82	16.3	54.3	40.9	86.0
stroke/tia	1	9	1.8	6.0	4.5	9.4
stroke	1	5	1.8	3.3	4.5	5.2
tia	0	4	0.0	2.6	0.0	4.2
venous thrombosis/phlebitis	0	20	0.0	13.2	0.0	21.0

We have the following comments on event rates in Table 4:

- As with CV deaths, rates that look bad by patient do not appear differentiated by PEY. The rates per PEY for any ischemic heart disease (including MI, angina, and general reports of ischemic or coronary heart disease) are not differentiated between Cimzia and placebo.

- There are few cases, but the available ones suggest a possible effect of Cimzia on heart failure. Such an effect is not inconsistent with the possible effects of other TNF blockers and, because of the low numbers, adds little to what is known about activities of TNF blockers in heart failure.

- We have included in "cardiac tachyarrhythmia" AE reports of tachycardia, so this event definition does not imply a serious arrhythmia. Of greater interest is the increased rate of atrial fibrillation. Note that two of the deaths were accompanied by atrial fibrillation. Atrial fibrillation is associated with increased risks of stroke and heart failure. While the stroke rates are not clearly differentiated between placebo and Cimzia, the combined stroke/TIA rates are. Stroke, of course, is strongly associated with hypertension (discussed next). Finally, if there is some direct cardiotoxic effect of TNF blockade responsible for worsening heart failure, we would not be surprised to have atrial fibrillation as part of the clinical picture.

- Clearly there are more hypertensive AEs reported for Cimzia than for placebo. The increased rates are confirmed by the incidence plots in Figure 3 and Figure 4.What is less clear is what these hypertensive AEs represent, i.e., timing relative to agent administration, severity, duration, etc. Three of the AEs, all in Cimzia groups, were reported as serious. We are aware of, but have not summarized here, the sponsor's

analyses that BP measurements done in the trials do not show increased mean or high outlier values—see our conclusions below.

Figure 3: Hypertension AEs by Dosing Group in the Phase 3 Cimzia Trials in RA

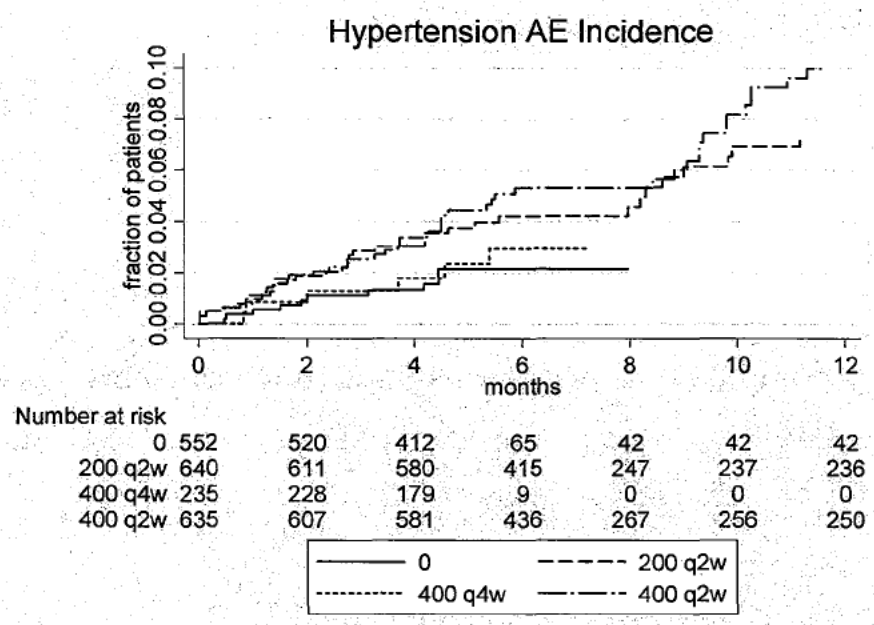
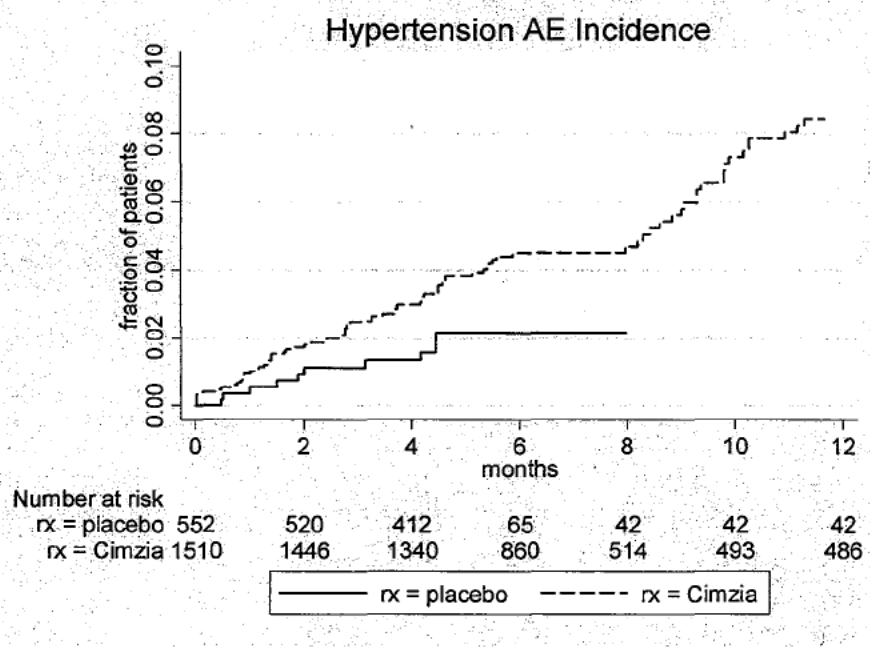


Figure 4: Hypertension AEs by All Cimzia vs. Placebo in the Phase 3 Cimzia Trials in RA



p = 0.016 by log rank test

- The venous thrombosis and phlebitis AEs were predominantly lower extremity events plus one event of inferior vena cava thrombosis and one event of cubital vein thrombophlebitis. The time-to-event analyses shown in Figure 5 and Figure 6 provide an estimate of the significance of this finding. Pulmonary embolism was rare, with one case each in the placebo and a Cimzia group. We note that the Enbrel label mentions deep vein thrombosis and thrombophlebitis, the Humira label leg thrombosis, and the Remicaide label thrombophlebitis, so this Cimzia finding may be one with which you are familiar.

Figure 5: Thrombophlebitis Incidence by Dosing Group in the Phase 3 Cimzia Trials in RA

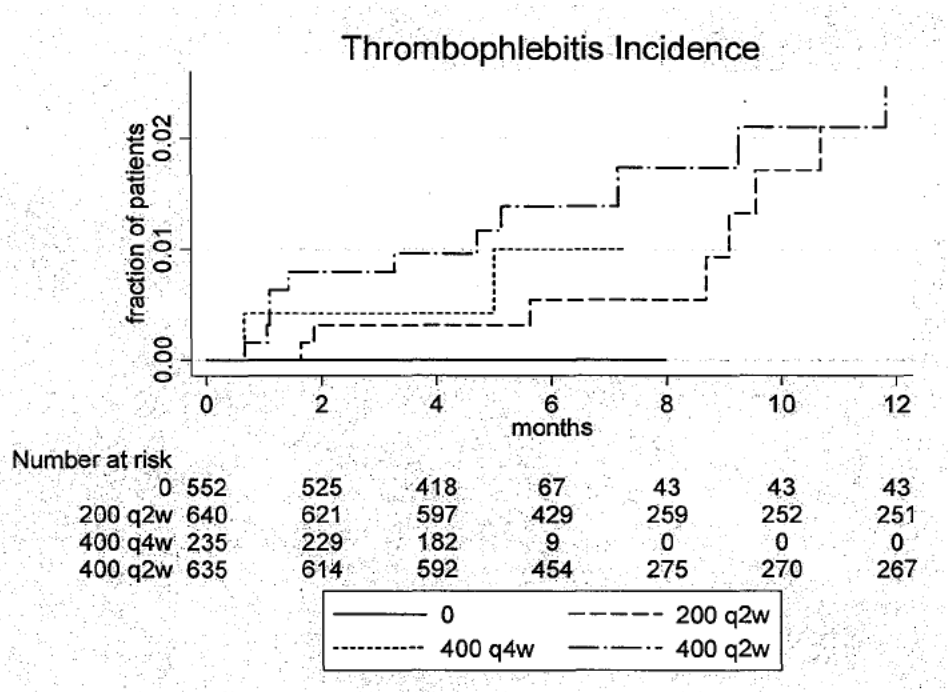
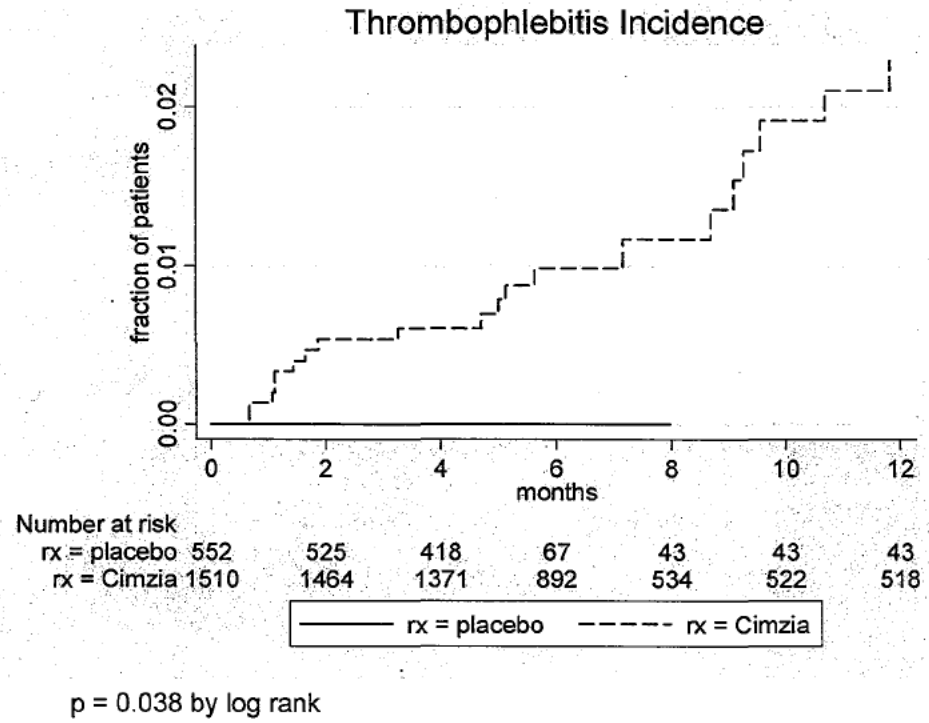


Figure 6: Thrombophlebitis Incidence by All Cimzia vs. Placebo in the Phase 3 Cimzia Trials in RA



p = 0.038 by log rank

We have the following conclusions and recommendations:

1. We do not believe that there is substantial evidence of a detrimental impact of Cimzia upon short term cardiovascular mortality or ischemic heart disease. We would not impose based on CV safety concerns any additional restrictions on use or investigational populations or additional monitoring requirements in trials.

2. The possibility of an adverse impact upon heart failure remains as for other TNF blockers. The current class labeling adequately expresses the potential risk. Further exploration or refutation of the potential for worsening heart failure would be facilitated by adding BNP and possible troponin measurements to any future clinical trials. However, the interpretation of any BNP or troponin changes would be difficult, so we view such monitoring as good experimentation and potentially adding to medical knowledge but not as a regulatory requirement.

3. Examining rates of atrial fibrillation and strokes in the other TNF blocker RA trials and for other indications (particularly any including older populations) would be helpful in elucidating whether there are any effects upon these rates. The atrial fibrillation rates are low (<1%) so that frequent ECGs would not seem justified. We do not have any other monitoring changes to recommend to address these conditions.

4. We do not consider the hypertensive AEs to be explained adequately with the current data presentations. We believe a much more detailed presentation of the cases is worthwhile, including severity, timing relative to Cimzia administration, time course, background medications, etc. Regarding the sponsor's analyses of BP measurements, we note that BP measurement problems can obscure effects even in dedicated trials of antihypertensives and less than optimal analyses can mask effects in BP safety analyses. The sponsor's analyses of end mean changes do not rule out an effect that is not sustained until the next dose. Doing the analyses appropriately, if the data are sufficient, is very time consuming, so we would prefer to consider such analyses after the hypertensive AEs are better described so that analyses may be tailored to any signals detected. We are not reassured by the sponsor's observations that the placebo rate is low in the Cimzia trials compared to trials of other biologics in RA because historical comparisons are unreliable and we believe that the most appropriate comparisons are the placebo-controlled parts of the double-blind, randomized Cimzia trials in RA.

5. We will leave the question of further exploration of the thrombosis/phlebitis rates to your discretion.

CLINICAL REVIEW

Application Type	BLA
Submission Number	125271
Submission Code	Not Applicable
Letter Date	November 29, 2007
Stamp Date	December 6, 2007
PDUFA Goal Date	October 5, 2008
Reviewer Name	Carolyn L. Yancey, MD
CDTL	Jeffrey N. Siegel, MD
Division Director	Robert A. Rappaport, MD
Review Completion Date	August 11, 2008
Established Name	Certolizumab pegol
(Proposed) Trade Name	CIMZIA®
Therapeutic Class	Tumor Necrosis Factor Inhibitor
Applicant	UCB, Inc.
Priority Designation	Standard
Formulation	200 mg liquid (1 mL) per vial in a prefilled single-use syringe
Dosing Regimen	400 mg sc at 0, 2 and 4 weeks, followed by 200 mg sc every other week
Indication	Rheumatoid Arthritis (RA)
Intended Population	Active RA unresponsive to MTX

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This biologic application license (BLA) 125271 is for the approval of the Tumor Necrosis Factor (TNF) blocker certolizumab pegol (CZP), Trade name CIMZIA®, for the proposed indications in adults with active rheumatoid arthritis (RA), unresponsive to methotrexate (MTX) and or other Disease Modifying Anti-Rheumatic Drugs (DMARDs), of reducing the signs and symptoms, major clinical response, inhibiting progression of structural damage, improving physical function, (b) (4) In addition, this licensing application proposes that CZP may be used in combination with methotrexate (MTX) or without MTX and other DMARDs. Four, global, Phase 3, randomized, double-blind trials (Studies 027, 050, 014 and 011) provide adequate evidence of efficacy and safety of CZP in patients with active RA. The majority of these enrolled patients had inadequate response to MTX or another DMARD.

This submission proposes that CZP is efficacious and safe in patients with RA who have experienced an inadequate response to MTX or other DMARDs. All four of these CZP Phase 3 trials provide evidence of CZP treatment effect in patients with active RA. The clinical development program for CZP included studies of 200 mg subcutaneously (sc) every 2 weeks (q2w) and 400 mg sc q2w with concomitant methotrexate (MTX) and a loading dose regimen of CZP at Week 0, 2 and 4. In addition, CZP 400 mg q4w with concomitant MTX and 400 mg without MTX or other DMARDs (monotherapy, Study 011) were studied. The majority of patients across these four trials were receiving concomitant MTX; one trial studied patients not receiving concomitant MTX (Study 011, CZP monotherapy).

CZP demonstrated clinical efficacy across these four Phase 3 trials based on the primary efficacy endpoint, the ACR20 response at 24 weeks. In addition, Study 027 employed the co-primary efficacy endpoint inhibition of progression of structural damage at 52 weeks as measured by the modified Total Sharp Score (mTSS) and provided evidence of radiographic inhibition. Inhibition of progression of structural damage was also assessed as the major secondary endpoint at 24 weeks in Study 050. CZP administered as 400 mg sc q4w with and without concomitant MTX (without a proceeding loading dose) also demonstrated evidence of efficacy based on the ACR20 response at 24 weeks.

The efficacy and safety data submitted in this application support the approval of this supplement under BLA 125271 for CIMZIA® for the signs and symptoms, major clinical response, inhibition of progression of structural joint damage and improving physical function in RA patients with revisions to the proposed labeling.

1.2 Risk Benefit Assessment

CZP demonstrated clinical efficacy for signs and symptoms across four Phase 3 trials (Studies 027, 050, 014 and 011) based on the primary efficacy endpoint - the ACR20 response at 24 weeks.

Efficacy for inhibition of progression of structural damage was demonstrated by the co-primary efficacy endpoint inhibition of progression of structural damage as measured by the mTSS at 52 weeks in Study 027 and by the major secondary endpoint at 24 weeks in Study 050. In addition, Study 027 provides evidence of a major clinical response. All four studies provide data that support the proposed claim of physical function response.

Overall, CZP was well tolerated and reflects a safety and efficacy profile similar to other approved TNF inhibitors. There was no increase in the all cause mortality with CZP treatment versus placebo (PBO). The types and incidence of malignancies observed during these trials are similar to those malignancies reported in the general RA population. In addition, the increased incidence of lymphomas observed across these studies, though increased compared to the general RA population, are consistent with the incidence of lymphomas reported with other TNF inhibitor therapies and with patients with active RA not receiving TNF blockers. There is a significantly increased risk of serious infection, including tuberculosis (TB), with CZP treatment compared to PBO control. The current labeling reflects the appropriate TB screening and careful monitoring necessary during treatment with CZP.

There was no cardiovascular signal observed across these four studies although there were a small number of heart failure events in the PBO-controlled and open-label (OL) studies. There was no observed increase in risk of congestive heart failure with long term exposure. The most common TEAEs were those observed commonly in the general RA population.

Based on these four trials, CZP is effective treatment for adults with active RA. In patients who have not completely responded to MTX, CZP 400 mg at weeks 0, 2, and 4, followed by 200 mg q2w was observed to be efficacious and was observed to provide a onset of action within the first week as shown in Study 027 and 050. There was no meaningful additional benefit with CZP 400 mg q2w compared to CZP 200 mg q2w. CZP 400 mg q4 (monotherapy) and CZP 400 mg q4w with concomitant MTX were observed to be efficacious although neither dose regimen demonstrated as rapid an onset of action or as large a treatment effect compared to CZP 200 mg q2w maintenance proceeded by the loading dose regimen. Study 014 (400 mg q4w + MTX) and Study 011 (400 mg q4w) did not employ a loading dose.

The liquid formulation intended for marketing was studied in Study 050. Overall, the liquid and the lyophilized formulations were observed to both demonstrate similar efficacy. In general, the incidence of adverse events (AEs) with the liquid formulation was lower than that observed with the lyophilized formulation.

If this supplement is approved for marketing, there would be two different formulations of CIMZIA® on the market [liquid in a prefilled single use syringe containing 200 mg (1mL) of

CIMZIA® and lyophilized powder (200 mg of CIMZIA® in a glass vial) for reconstitution with 1mL sterile water for injection].

1.3 Recommendations for Postmarketing Risk Management Activities

CIMZIA® already has a Medication Guide (MedGuide) and a Risk Evaluation and Mitigation Strategy (REMS). Apart, from the routine Pharmacovigilance, no additional postmarketing risk management activities are warranted.

1.4 Recommendations for other Post Marketing Study Commitments

There are currently three other approved TNF blockers. The safety of this class of products is well characterized and described in the product labeling. The safety of CIMZIA® is similar to what is seen with the other TNF blocker products. Apart from the issue of studies in children and adolescents with polyarticular subtype of moderate to severe juvenile idiopathic arthritis (JIA), no other postmarketing study commitments are warranted. The issue of safety and efficacy studies in children and adolescents will be discussed with the Pediatric Review Committee (PeRC) on September 24, 2008.

2 Introduction and Regulatory Background

2.1 Product Information

CIMZIA® is certolizumab pegol (CZP), a pegylated genetically engineered humanized monoclonal antibody Fab' fragment derived from a murine hybridoma, with specificity for tumor necrosis factor-alpha (TNF-α, TNF). CZP binds to TNF, thereby, inhibiting TNFs role as a key mediator of the inflammation and joint destruction associated with rheumatoid arthritis (RA).

CZP was first approved by the Food and Drug Administration (FDA) on April 22, 2008 for reducing the signs and symptoms of Crohn's Disease and maintaining clinical response in adult patients with moderately to severely active disease with inadequate response to conventional therapy. The labeling for CIMZIA in Crohn's Disease is 400 mg subcutaneously initially and at Weeks 2 and 4; if response occurs, follow with 400 mg sc every four weeks.

CZP is available in Switzerland as of 03January2008 for patients with Crohn's Disease following the approval by the Swiss health authority, Swissmedic, on 07September2007. Note: post-marketing data are not included in the 120-DSU in this review since the product was launched after the safety cutoff date of 30November2007.

Early in the RA clinical development program, the non-clinical studies and the Phase 1 and 2 studies employed a liquid CZP formulation (acetate buffer (b) (4) for intravenous (i.v.) infusion (20 mg/mL) and subcutaneous (sc) injection (200 mg/mL). The 400 mg dose was administered as 2 injections of 200 mg each, administered at separate injection sites. The sponsor developed a

lyophilized powder in 2003 for reconstitution and administration by sc injection (200 mg/vial, lactate buffer pH 5.2). This latter formulation was employed in three of the four Phase 3 RA studies (Study 027, 014, and 011). A ready-to-use liquid formulation as (200 mg/mL, acetate buffer pH 4.7) was developed in 2005 and is the current proposed commercial formulation for sc administration.

The proposed commercial formulation is the liquid employed in Study 050. A bioavailability study (Study 038) was conducted to support the comparability between the lyophilized and liquid formulations. Most recently (2007), a prefilled glass syringe (1 mL; 200 mg/mL) for self-administration is proposed for the commercial dosage form in RA. The proposed commercial product is a single use, prefilled glass syringe fitted with a staked 25G x ½" thin wall needle. (b) (4) The drug product is manufactured at (b) (4).

The proposed CZP dosage and administration for patients with active RA is 400 mg at weeks 0, 2 and 4 followed by 200 mg every other week. The alternative CZP dose of 400 mg every 4 weeks can be considered as a maintenance dose. Labeling also proposes that CZP may be used alone or in combination with methotrexate.

As of this submission on November 29, 2007, there have been 10 clinical trials in patients with active RA: one drug-drug interaction study, two-dose finding studies, four adequate and well-controlled Phase 3 clinical studies, and three ongoing open-label long-term follow-up studies. Use of the prefilled syringe is supported by the open-label Substudy 051 demonstrated that patients can safely self-administer CZP from the prefilled syringe.

2.2 Tables of Currently Available Treatments for Proposed Indications

Physicians select drug products or biologic therapies based on the severity of the patient's disease. Typically, the early RA treatment regimen includes initial therapy with a non-selective COX-2 inhibitor non-steroidal anti-inflammatory (NSAID) drug product and may be expanded to include a DMARD, biologic, and or corticosteroid, as needed. NSAIDs and COX-2 inhibitors are primarily administered for symptomatic relief of pain and are useful concomitant therapies because of their anti-inflammatory and analgesic effects. DMARDs are typically administered to reduce the signs and symptoms of RA as well as reduce the radiographic progression of joint damage.

The most commonly prescribed non-biologic DMARDs administered for the treatment of RA are methotrexate (MTX), sulfasalazine (SSZ), hydroxycholorquine (HCQ) and leflunomide (LEF). LEF has demonstrated clinical benefit similar to MTX or SSZ. The use of LEF is more limited due to the gastrointestinal side effects and the potential risk of teratogenicity. MTX is the most commonly prescribed first-line DMARD because of its proven clinical benefits and well-known long-term efficacy as well as known toxicity profile in RA patients. Alternatively, SSZ and HCQ may be employed for the treatment of milder RA. Remission may not be achieved with a single standard DMARD therapy, therefore, many different two- and three-drug combinations of DMARDs have been found to be more effective than MTX therapy alone.

The currently approved biologic products for RA are DMARDs based on large clinical trials demonstrating that the biologic products can inhibit the progression of joint damage. MTX is frequently the initial DMARD which is most often combined with a biologic TNF inhibitor, such as Enbrel® (etanercept), Remicade® (infliximab) or Humira® (adalimumab). Large controlled clinical trials have demonstrated that TNF inhibitors administered concomitantly with MTX are superior to MTX administered alone in patients with moderate to severe RA. The TNF inhibitors have achieved inhibition of structural progression over clinical trial durations of one year with long-term durability of effect demonstrated out to 5 years.

The fusion protein, Orencia® (abatacept, CTLA-4Ig) is approved for the treatment of signs and symptoms of moderate to severe RA, major clinical response (ACR70), and inhibition of structural progression. Rituxan® (rituximab) is approved for the treatment of moderate to severe RA refractory to other DMARDs. Kineret® (anakinra) is the single human recombinant anti-IL-1 receptor antagonist that is approved for the treatment of RA. Overall, the clinical trials with anakinra demonstrated a small effect size compared to TNF-inhibitors.

2.3 Important Safety Issues with Consideration to Related Drugs

The major safety risks with administration of TNF-inhibitors in the treatment of patients with RA are the increased incidence of infections and the potential risk of developing malignancy with a specific concern for the potential development of lymphomas. These and other safety issues such as hypersensitivity reactions and other safety concerns, as it may relate to the presence of antibody to the biologic product, are discussed in Section 7.0 of this review.

2.4 Summary of Pre-submission Regulatory Activity Related to Submission

CZP was developed by Celltech Research & Development (R&D), Ltd. UK (now UCB, Inc) and licensed to Pharmacia (acquired by Pfizer) to conduct the clinical trial development program for rheumatoid arthritis (RA). Subsequently, the responsibilities for the RA clinical development programs were given to UCB, Inc.

- The first submission for CZP occurred in June 2001. Pharmacia filed an IND (9,869) to support clinical trials of CZP in patients with RA.
- February 19, 2002, clinical EOP2 meeting discussed the need to obtain antibody titers four-to-five half-lives post injection and gather immunogenicity data on patients who have been re-exposed to CZP. The CZP 800 mg dose should be assessed for safety and efficacy before the BLA submission. The total number of patients to be studied should be a minimum of 1000 to 1500 patients treated for at least one year.
- November 7, 2002, a teleconference following discussion with Dr. Jeffrey Siegel about Phase 3 protocols was conducted. The following agreements were reached: 1) a 12-month double-blind trial should be followed by an open-label extension study to demonstrate improvement of physical function (HAQ); at the time, Dr. Siegel considered fatigue a reasonable and distinct measure as long as it is validated in RA patients, and stated that the vitality domain of the SF-36 has been used as a measure of fatigue and results have appeared in the label of other products; 2) the SF-36 is an acceptable measure for Health

Related Quality of Life and the SF-36 physical component summary (PCS) corroborates the HAQ. The SF-36 mental component summary (MCS) would not be expected to improve but be maintained. Health Outcomes endpoints do not necessarily need to be defined as primary endpoints; (b) (4)

- On February 13, 2004, Celltech requested that the company sponsorship transfer IND 9,869 from G.D.Searle (Pfizer) to Celltech R&D Limited.
- In May 2004, Celltech was acquired by UCB Pharma, Inc. and the company name change for the IND was submitted in March 2005.
- (b) (4) .
- On October 27, 2004 (Type B meeting for IND 9,869), Celltech met with the Center for Biologic Evaluation and Research (CBER) to discuss additional Phase 3 studies and the issues of the comparability strategy. CBER recommended that Celltech develop clinical trials to demonstrate the same treatment effect for the CZP 400 mg q2w compared to CZP 200 mg q2w and to provide supportive evidence for the proposed CZP 400 mg q4w trials. CBER recommended that adequate analysis should be submitted to conclude that the CZP 200 mg q2w regimen provides similar exposure to CZP 400 mg monthly regimen. Appropriate pharmacokinetic analysis should be submitted for the proposed dosing regimens. The sponsor completed two additional Phase 3 clinical studies, one of 52 weeks (Study 027) and one of 24 weeks (Study 050) to support the CZP 400 mg q2w dose regimen.
- October 27, 2004, CBER agreed regarding the use of two formulations (lyophilized and liquid) in the two proposed Phase 3 studies, supported by an appropriate comparability package based on comparison of the liquid and lyophilized formulations. The proposed commercial formulation is the liquid used in Study 050. A lyophilized formulation was used in the three other Phase 3 studies (Study 011, 014 and 027). The prefilled syringe should include graduations on the syringe and the submission should be supported by information on the number of patients who can safely self-administer the drug to show easy handling and administration of the syringes.
- It was agreed between CDER and UCB, Inc. that an appropriate safety database would be approximately 1,500 RA patients with 6 months of exposure and over 1,100 RA patients with over one year exposure.
- August 2005, FDA notified UCB of a partial clinical hold due to manufacturing breech that allowed solvents from another product to be introduced into manufacturing campaigns of CZP.
- September 1, 2005, a complete response to the partial clinical hold was provided. FDA subsequently notified UCB that the partial clinical hold was lifted September 15, 2005.
- November 2006, FDA requested additional information regarding tuberculosis adverse events in RA patients.
- December 2006, UCB provided a preliminary assessment of the tuberculosis events.
- February 16, 2007, a complete response to this request was sent to the Agency.

- March 2007, UCB was notified of suspected fraud and misconduct at a clinical trial site in Lithuania by the State Medicines Control Agency (SMCA) which was performing a routine audit of Dr. Paksys' Good Clinical Practices. UCB immediately conducted a For Cause audit of the site and found that patients were included in studies which did not meet the eligibility criteria and that serious adverse events and deaths were unreported by the site. UCB closed the site and the replacement investigator was asked to perform termination and follow-up visits for each patient involved in the study. UCB notified the Agency and the Division of Scientific Investigations (DSI) of the preliminary findings on 30 March 2007 and performed a full investigation of the site which resulted in completed audit findings that were provided to FDA in May 2007.
- June 2007, Pre-BLA meeting with the FDA/CDER/DAARP was conducted. Agreements and discussions included the following: 1) endpoints and the responder definitions in the Phase 3 trials were considered acceptable; (b) (4) ; the Division recommended that the sponsor submit a dossier to IND 9,869 to evaluate the (b) (4); 3) BLA must provide evidence of bioequivalence of the lyophilized formulation versus the liquid formulation; 4) mono-therapy, CZP 400 mg q4w without concomitant MTX, could be supported by one adequate and well-controlled study, in addition to two adequate and well-controlled Phase 3 studies of CZP with concomitant MTX in RA patients with active disease. The Division recommended that the proposed label be a simple statement without claims and qualifiers; 5) agreement was reached for the presentation of radiographic data to support "inhibition of the progression of structural damage" in the label; 6) FDA agreed that the Integrated Summary of Safety would contain analyses restricted to the RA population; UBC, Inc. has provided adequate explorations for the dose response of CZP in an adequate number of patients with active RA. Note: in the RA development program, there were 2,367 unique patients yielding a total exposure (patient-years) of 3,997.6 (4000.5); 7) UCB presented the self-administration injection questionnaire to the Division and the Division explained that the proposed minimum number of patients seems small and a sample size of at least 50 patients may be more appropriate. FDA requested that the SIAQ results be submitted with the original BLA. It was also requested by the Division that UCB provide information within the BLA to support the lack of overfill in the pre-filled syringe to ensure accurate dosing; 8) agreement was reached regarding submission of an electronic hybrid BLA as the sponsor explained they were unable to submit the BLA in eCTD format by November 2007.

2.5 Other Relevant Background Information

All relevant background information is incorporated into the appropriate section of this review.

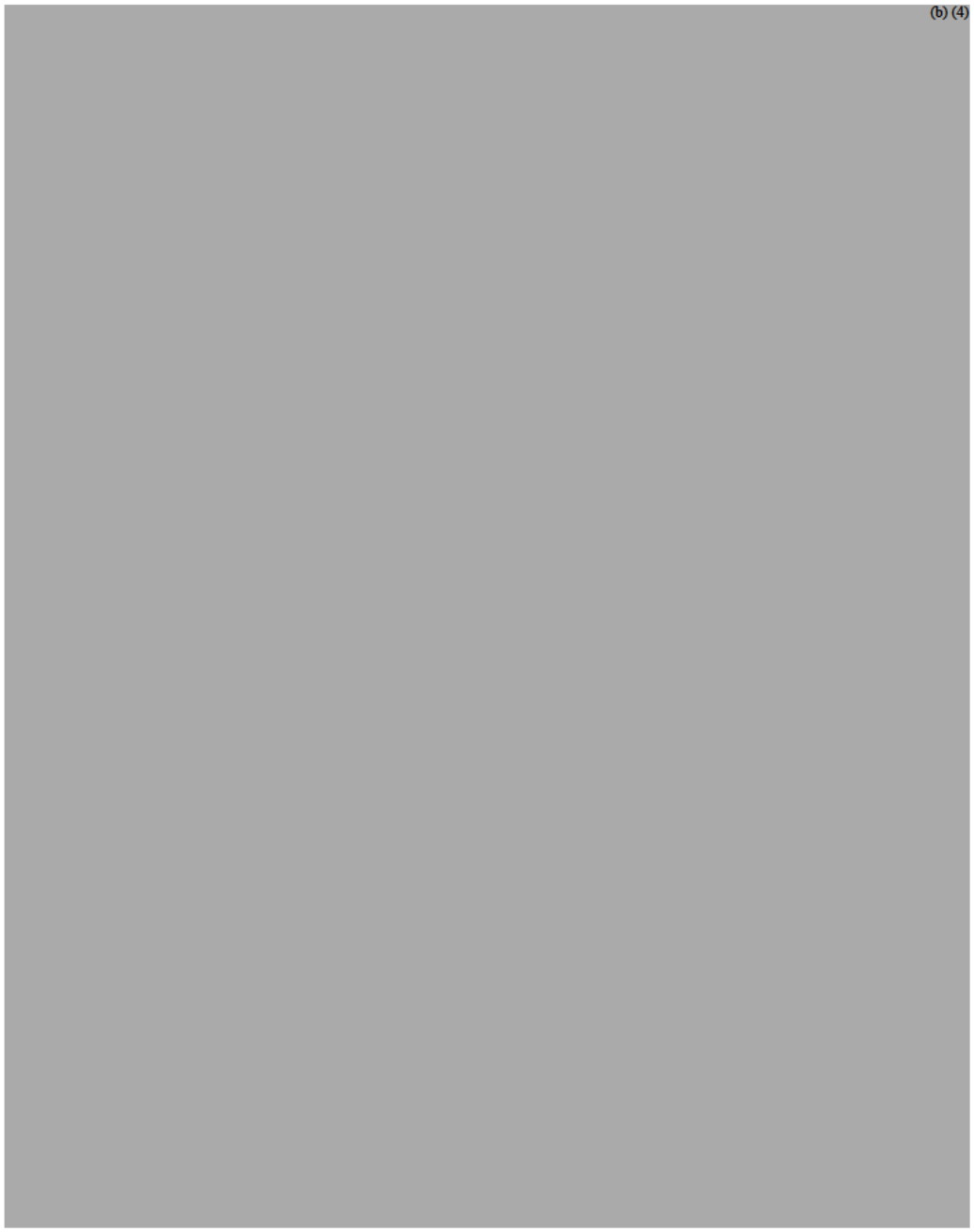
3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the monitoring appeared adequate and these data from these trials had relatively little missing data.

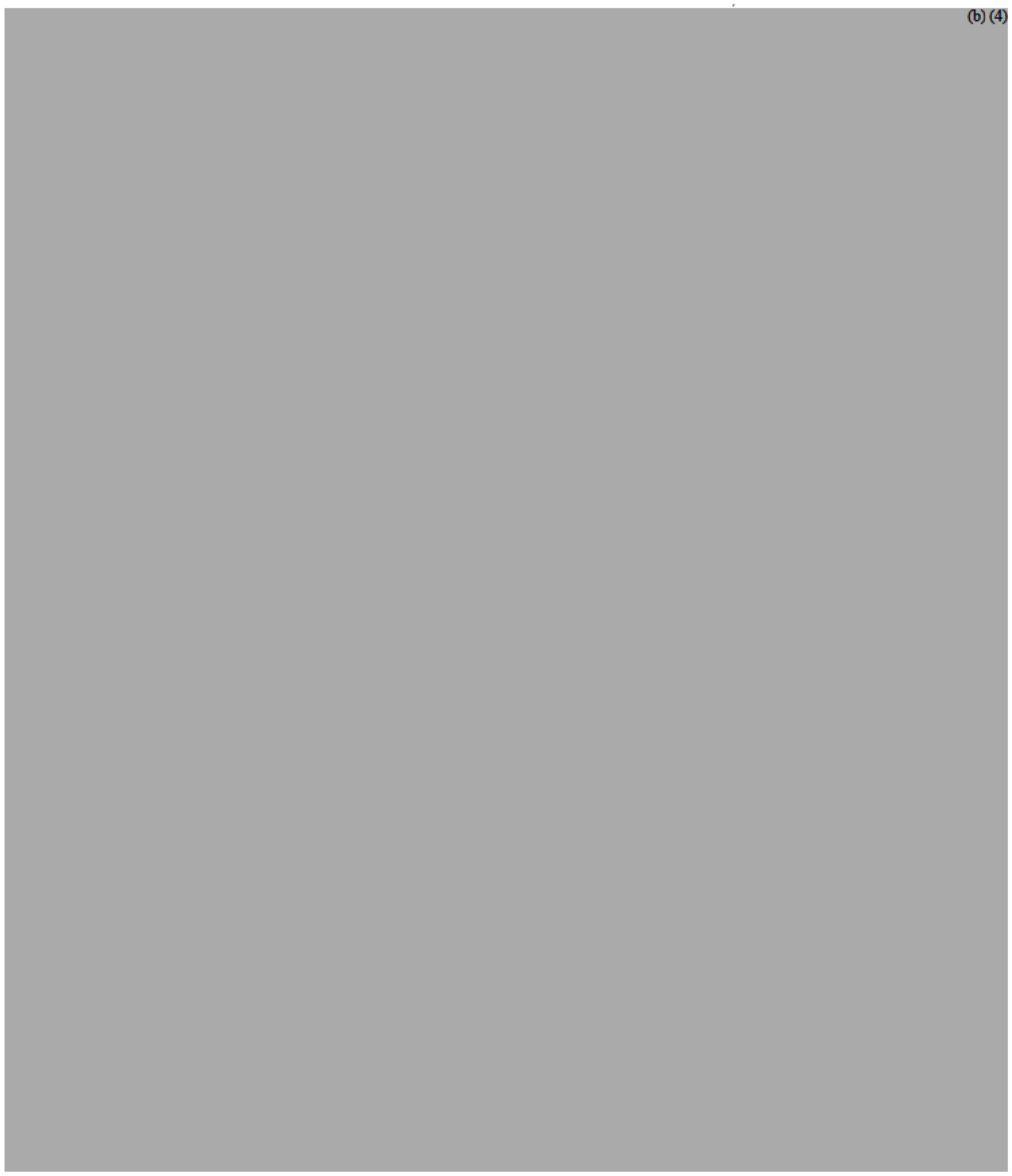
Study 027
Study 027 was conducted in 147 centers across 22 countries. Due to documented fraud and misconduct at Site 93 in Lithuania, these data from this site were excluded from the safety and efficacy analyses completed.

Prior to the initiation of this study, Celltech was the developer of CZP and was the initiator of this study. During the conduct of Study 027, Celltech was acquired by UCB Pharma SA, who then continued the CZP RA clinical development program. Study 027 was conducted and analyzed by UCB Inc. The Contract Research Organizations (CROs) employed in Study 027 are listed in **Table 1**. The audit certificates for this study were submitted in the BLA submission.



Study 050

This study was conducted in 76 sites in 13 countries from June 2005 to September 2006. Due to questionable data and a serious breach of Good Clinical Practice (GCP) at one site, Site 104 in Lithuania, these data were not included in the analyses performed. The CROs employed to provide diverse responsibilities for the conduct of this study are listed in **Table 2.** The audit certificates for this study were submitted in the BLA.



Study 014

This study was conducted in 43 sites in 7 countries from October 2002 through January 2004. CZP was discovered by Celltech, Ltd. By way of agreement between Pharmacia and Celltech, Ltd., Pharmacia initiated and sponsored Study 014. During the course of this study, Pharmacia was acquired by Pfizer. In December 2003, Celltech, Ltd. retained CZP and acted as the sponsor until the conclusion and database lock of Study 014. Blinded monitoring activities were initially carried out by Pharmacia and completed by Pfizer's clinical research associates (CRAs). The sponsors were responsible for the regulatory compliance and the quality assurance. Unblinded monitoring activities of the study medication preparation were carried out by (b) (4) . In August 2004, UCB acquired and merged with Celltech, Ltd. The study was initiated by Pharmacia under the protocol number CDP 877-IFL-0587-014. Following the transfer of responsibilities to Celltech, the study was referred to as Study 014 and this

terminology has been used in all regulatory correspondence and filings. The CROs employed to support Study 014 are listed in **Table 3.** The audit certificates for Study 014 and 011 were submitted in the BLA submission.

Study 011
This study was conducted in 36 sites in 3 countries from June 2003 through July 2004. During the course of this study, Pharmacia was acquired by Pfizer. Effective February 22, 2004, Celltech, Ltd., retained CZP and acted as the sponsor until the conclusion and database lock of this study. In August 2004, UCB acquired and merged with Celltech, Ltd. The sponsors were responsible for regulatory compliance and quality assurance. Study 011 was initiated by Pharmacia under the protocol number CDP 877-IFL-0587-011. Following the transfer of responsibilities to Celltech/UCB Pharma, the study was referred to as CDP870-011 and this terminology was used in all regulatory correspondence and filings. The CROs employed to support Study 011 are listed in **Table 3.**

3.2 Compliance with Good Clinical Practices

All of the CIMZIA clinical trials in the RA development program were carried out in accordance with the ICH notes of the Guidance on good Clinical Practice (ICH/CPMP/135/95), the requirements set forth in the US FOOD and Drug Administration (FDA) Code of Federal Regulations 9CFR) Title 21, the Declaration of Helsinki as adopted by the 18th World Medical Assembly (1964), revised by Tokyo (1975) and amended in Venice (1983), Hong Kong (1989),

South Africa (1996) and Edinburgh (2000), and applicable local regulatory requirements and laws.

While investigators were instructed to conduct the study according to the GCP guidelines, there may have been isolated instances where they were not followed completely. Before the start of the study, the clinical investigators were instructed about the study conduct according to the protocol, GCP, and applicable laws/regulations. The clinical investigators allowed the sponsor or designee to review periodically, at mutually convenient times during and after the study, all CRFs and the corresponding source documents. The monitoring visits provided the sponsor or designee the opportunity to evaluate the progress of the study to verify the accuracy and completeness of CRFs, and to ensure that all protocol requirements, applicable authorities' regulations and clinical investigator obligations were fulfilled, and to resolve any inconsistencies in study records. Two independent operators double entered all the CRF data into an electronic database by means of a clinical data management system. After reconciliation of the double-entered data, an electronic audit trail system was set up to track all subsequent data changes. Regular back-ups of the electronic database were carried out.

In addition to a systematic and manual review of the data, computerized checks were also performed to identify any discrepancies in the data. In case of missing or inconsistent data, appropriate queries were addressed to the study monitor. Investigators were contacted when needed. Pending queries were discussed during a pre-analysis meeting and appropriate action was taken to resolve queries before locking the database.

[redacted] (b) (4) According to the sponsor, this audit was in response to reports from UCB study team personnel that specific issues were identified in data transferred to UCB (b) (4) Those issues were investigated during this audit and were specifically used as a starting point for inspection of (b) (4)

The auditors concluded that a number of (b) (4) experienced critical failures, and that not all contracted agreements between UCB and (b) (4) had been performed. The purpose of the audit was to investigate issues identified by UCB from X-ray score data transfers sent to UCB (b) (4) . The audit was conducted by one independent consultant to UCB, one UCB Quality Assurance auditor, and two UCB Clinical Data Managers.

Audit of (b) (4) (Study 027 and 050) included the following:
- The CZP 027 Remote Computer Assisted Masked Reading (CAMR) system had not been formally validated. The CAMR is the image display and database review system.
- Audit trailing functions were not programmed to provide reviewable access for evaluators.
- It was not possible during the audit to determine if adequate testing was performed and documentation maintained for validation of the (b) (4)
- The X-ray Charter indicates that (b) (4) will Quality Check the image reading interpretation before each database transfer to UCB. At the time of this audit, (b) (4) had not performed any QC checks for CZP 027 and CZP 050.

- The CZP 050 Charter was still in draft form at the time of this audit and the reading of films was in progress.
- (b) (4) had not programmed a systematic quality check to assure that the interrelated systems (b) (4) were functioning as expected.
- Export from the CAMR database to SAS data sets was performed using an intermediate Microsoft Access file. Data in Microsoft Access tables are modifiable without generation of an audit trail. This process does not allow for proper security measures to ensure transferred date has not undergone change.

Actions taken from the (b) (4) Audit:
The following actions were taken in response to this audit:
- (b) (4) performed a retrospective validation of the CZP 027 CAMR
- (b) (4) tested the audit trail function and it was concluded that data in the audit trail were reliable and accurate.
- (b) (4) provided validation documents demonstrating that the Nuntio system had been validated.
- (b) (4) performed a Quality Check on 10% of all image reading interpretations.
- The CZP-050 Charter was finalized on 13Nov2006.
- (b) (4) provided documentation to UCB demonstrating that a systematic quality check is performed by their Core Lab and Data Management groups to ensure their systems are functioning as expected.
- (b) (4) confirmed that the CAMR database and SAS data sets are on a network location that is accessible only to the Clinical Data Management group. The MS Access file is used only as a bridge between the SQL Server database (source) and SAS; nothing ever gets written to this file after it is created.

UCB determined that the follow-up actions taken by (b) (4) were appropriate.

Lithuanian Site Audit
In February 2007, following the generation of the Study report analyses, UCB received notification from (b) (4) that the State Medication Control Agency (SMCA) under the Ministry of Health Care of the Republic of Lithuania had suspended R. Paksys, M.D., from further participation in clinical trials. Dr. Paksys was the Principal Investigator at Panevezys Hospital (Site #093 in Study 027 and Study 028 and Site #104 in Study 050 and Study 051 for the conduct of 4 CZP studies. The SMCA's decision was based on a routine GCP audit of the site earlier that same month. As a result of this information, UCB and (b) (4) conducted a joint "for cause" audit of the site in March 2007. Due to issues detected during the audit, it was decided to exclude this site's data from analysis with that of the rest of each study population. It was also decided, in the interest of patient safety, that the patients at the site should be discontinued from the trial under the direction of the new Principal Investigator (Violeta Smilgiene). Following UCB's notification of their March audit findings to SMCA and the Lithuanian Bioethics committee, the Lithuanian Office of national Drug Control Policy

conducted a "for cause" audit. The results, which were shared with UCB in June 2007, were consistent with UCB's findings.

Audit findings from the four Phase 3 CZP studies included the following:
- Failure to report a significant number of SAEs, including 2 deaths during Study 051. Prior to the site audits, no SAEs were reported for any patients in any of the studies.
- In Study 050, the substitution of new patients for those 2 unreported deaths and for a patient who had withdrawn from the study.
- In Study 050, revised informed consent forms were signed by the substitutions as if they were assuming the identity of the previous subjects.
- The source documents created for the study were not consistent with the original outpatient clinic records.
- Dr. Paksys did not typically provide the original outpatient clinical records for review during the study. When these records were obtained during the audits, they listed AEs that were not captured on the CRFs.
- Four of the 15 subjects enrolled in Study 050 did not meet the inclusion criteria.
- Nine patients (5 in Study 028 and 4 in Study 051) participated in an experimental influenza vaccine trial concurrent with the long-term CZP study and, thus, were included in 2 trials of investigational products at the same time.
- Study medication records indicated subjects had received investigational product on the date of discontinuation from the study when, in fact, the study medication had been discarded according to the study nurse.
- While subjects were hospitalized drug accountability records indicated that they continued to receive study medication. Doctor's orders had not been written to administer the study drug nor was it indicated in the hospital records that the study medication had been administered.

The Sites (#104 and #093) data were excluded from the primary safety and efficacy analyses for the ACR20 at Week 24.

The Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) requested a consult from the Division of Scientific Investigations (DSI). This consult confirmed the above cited serious violations and biases as reported by the sponsor. In addition, DAARP requested a consult from the Division of Medical Imaging and Hematology Products (DMHIP) to review two Independent Radiology Review Charters (IRCs) submitted in support of the Study 027 and 050. Overall, DMHIP reported that the provisions of the charter were generally acceptable as were the interpolation/imputation processes employed by (b) (4)

In summary of the sponsor's compliance with GCP, some of the findings were serious violations, however, the sponsor's monitoring adequately detected these issues and addressed them appropriately and expeditiously indicating due diligence. In general, the violations would not be expected to impair the interpretability of the data.

3.3 Financial Disclosures

UCB, Inc has adequately submitted the Certification: Financial Interests and Arrangements of Clinical Investigators Forms (Form FDA 3454) for Study CDP870-111, CDP870-027 and CDP870-050 and the individual investigator Certification/Financial Disclosure Forms (Form FDA 3455) by Clinical Investigators. One clinical investigator with Study CDP870-011 acknowledged financial stock valued in excess of $50,000. Our review did not find evidence of bias in the results of Study 011. By way of response to an Information Request (04April08), acceptable financial disclosure information and the complete clinical investigator list was received by the Agency for Study 014 and found to be acceptable. No financial conflicts of interest were found that would impair the interpretability of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CZP is a recombinant, humanized Fab' antibody fragment directed against TNF-∝, covalently bound to PEG2MAL40K, (b) (4) . CZP neutralizes the biological activity of TNF-α. (b) (4) The CZP Fab' fragment is produced in *Escherichia coli*. The light chain is composed of 214 amino acid residues and the heavy chain is composed of 229 amino acid residues. (b) (4) The schematic of the CZP drug substance is shown in **Figure 1.** See the Chemistry Manufacturing Control (CMC) review by Gupreet Gill-Sangha, PhD and Barbara Rellahan, PhD.

4.2 Clinical Microbiology

Under BLA 125271 for CIMZIA® in RA, there were no clinical microbiology related issues.

4.3 Preclinical Pharmacology/Toxicology

The non-clinical developmental strategy for CZP, as explained by the sponsor, was based on the pharmacological activity and selectivity of the molecule and the intended subcutaneous clinical route of administration. The program is consistent with the ICH S6 Guidance "Pre-clinical Safety Evaluation of Biotechnology Derived Pharmaceuticals" (ICH S6 1997). In addition, all bio-analytical methods used to support the safety studies were validated in accordance with the ICH Q2A and Q2B Guidance. All non-clinical safety studies were performed in accordance with "Good Laboratory Practice" as described in the US. Federal Register (FDA) dated 22 December 1978 and the "OECD Principles of Good Laboratory Practice" concerning Mutual Acceptance of Data in the Assessment of Chemicals dated 26 November 1997. Quality Assurance statements were provided by the sponsor in the reports of all non-clinical safety studies.

- The neutralizing activity of the antibody against TNF-α from a range of species was investigated (human, Cynomolgus monkey, rhesus monkey, baboon, dog, rabbit, guinea pig, rat and mouse). These studies confirmed the specificity of CZP for human TNF-∝ and were used as the basis for the selection of species for the non-clinical efficacy and safety testing.

- The *in vivo* pharmacodynamic activity was explored and documented in models based on human TNF-∝ (induced responses and the pivotal toxicity studies), consisting of single dose and repeat dose studies of 4 weeks, combined 13/26 weeks and 52 weeks) were conducted in the Cynomolgus monkey.

- Similar to other monoclonal antibodies and to marketed TNF-α inhibitors, no conventional carcinogenicity testing was performed with CZP. The rationale for this decision being that the

studies cannot be dome due to immunogenicity and the lack of pharmacological activity of CZP in species normally used for carcinogenicity testing.

- In order to assess the effects of long term TNF-α inhibition on immune function and to evaluate any proliferative effects on lymphoid tissues (in particular lymphoma formation), a 52-week study was conducted in Cynomolgus monkeys with a 26 week treatment-free period. Although not routinely performed for antibodies, a standard package of genotoxicity studies was conducted to support the safety assessment of CZP, which incorporates a linker-PEG construct.

In summary, the key factor contributing towards the mode of action of CZP in RA is likely to be neutralization of soluble and membrane TNF-∝ (mTNF-α) mediated effects, without any associated killing of TNF expressing cells. By blocking TNF-α, CZP has the potential to block cytokine production from cells. In contrast to other anti-TNF agents, CZP did not increase the proportion of apoptotic T-lymphocytes or monocytes, cause neutrophil degranulation or cell death, and did not activate antibody dependent cell cytotoxicity and complement-mediated cytotoxicity.

- The PEGylation of the Fab' fragment, to produce CZP, resulted in an extended absorption phase from the subcutaneous space and a slow elimination phase from the circulation when compared to the non-PEGylated Fab'. These studies showed CDP870 to be well tolerated with no findings of toxicological significance.

- CZP showed no genotoxic activity and, although no specific carcinogenicity studies were conducted, a 52-week monkey study showed no effects on lymphoid tissue or lymphocyte subset counts.
- No adverse effects were seen in the reproductive studies following sustained TNF-α suppression. These findings, along with absence of any reproductive organ pathology in the chronic toxicity studies, do not provide any signals that suggest that CZP would be a hazard to man under the proposed clinical use. See the Pharmacology toxicology review by Gary Bond, PhD.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

CZP binds to TNF-α, inhibiting its role as a key mediator of the inflammation and joint destruction associated with rheumatoid arthritis (RA). CZP has shown no histological cross-reactivity with a panel of normal human tissues that suggests the targeting of any tissue components, does not neutralize tumor necrosis factor beta (TNF-β, lymphotoxin) and does not activate complement or kill cells via antibody-dependent cell-mediated cytotoxicity. See Clinical Pharmacology review by Christoffer Tornoe, PhD and Srikanth Nallani, PhD.

4.4.2 Pharmacodynamics

The pharmacokinetic (PK) and pharmacodynamic (PD) analysis for CZP employed data from Studies 004, 011, 014, 027 and 050 in patients with active RA to assess the exposure-response relationship for the primary efficacy endpoint, the ACR20 response. The PK/PD model employed the population PK model from the assessment of CZP to predict the individual patient concentrations. The average plasma concentration (Cavg) was found to be superior to the individual predicted plasma concentration at the time of the ACR score assessment to enable the best fit, and was therefore used in the final model. MTX was a non-significant covariate in the exposure response model.

The PK/PD model was used to perform simulations to support the choice of the recommended CZP loading dose regimen 400 mg at Weeks 0, 2 and 4, followed by the maintenance dose 200 mg q2w. In summary, the PK/PD model showed that the most of the theoretical maximum response rate was achieved using the 200 mg q2w dose regimen. The average plasma concentration predicted for the individual patient during the dose interval (Cavg) provided a better exposure-response PK/PD model fit than the plasma concentrations at the time of observation, regardless of the dose interval (q 2 or q 4 weeks).The loading dose regimen was critical for improvement in the earlier onset of ACR response predicted for an individual patient. Simulations based on the exposure-response model predicted similar ACR response rates for the liquid and lyophilized formulations in ACR 20 response rate at Week 24. See the Clinical Pharmacology review by Christoffer Tornoe, PhD and Srikanth Nallani, PhD.

4.4.3 Pharmacokinetics

The Healthy Volunteer studies (Study 001, i.v.; Study 003, sc and iv; and PH 004) sc showed that single iv and sc doses of CZP demonstrated predictable dose-related plasma concentrations with a linear relationship between the dose administered and the C_{max} and the AUC. Overall, the PK parameters were similar with sc and iv route of administration. See Clinical Pharmacology review by Christoffer Tornoe, PhD and Srikanth Nallani, PhD

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The CZP clinical development program in RA as shown in **Table 4** was designed to support the following proposed indications and claims in adult patients with active RA, administered with background MTX or administered as monotherapy: 1) reduction in the signs and symptoms of RA, 2) inducing major clinical response, 3) inhibiting the progression of structural damage, and 4) improving physical function, (b) (4) As shown in **Table 5**, there are four completed Phase 3 double-blind, placebo (PBO)-controlled clinical trials which comprise the key studies of this review. Study 011, 014 and 050 were each 24 weeks in duration and Study 027 was 52 weeks in duration. All four studies are proposed to support the indication of the reduction of signs and symptoms of RA and Study 027 is proposed to support the additional claim of inhibition of the progression of structural damage with Study 050 as a supportive study for this claim. Improving physical function (b) (4) are supported by all four Phase 3 studies.

Study 027, 050 employed CZP 200 mg and 400 mg sc q2w treatment groups with background methotrexate compared to PBO + MTX. Study 011 was the single monotherapy trial with CZP dosing 400 mg sc q 4wk compared to PBO. Study 014 employed CZP sc q4w + MTX dosing compared to PBO + MTX.

There are three OL long-term extension trials (Studies 028, 051 and 015) which remain open pending a regulatory decision from the FDA for this BLA (125271).

Table 4: Clinical Trials in the CZP RA Clinical Development Program

Study Number	Design	Treatment Dose	Dose Frequency /Route	Study Duration	No. of Subjects[a]
Pharmacokinetic and MTX Interaction					
PHA-001	Open-label, PK interaction study with MTX	CZP[b] 400 mg	Single dose sc		16
Dose Finding					
CDP870-002	Double blind, placebo-controlled, single ascending dose study, with optional open-label second dose	CZP[b] 1 mg/kg, 5 mg/kg, or 20 mg/kg or Placebo	Single dose iv	16 weeks	36
CDP870-004	Two-panel, placebo-controlled, parallel-group, dose-ranging study, with open-label extension	CZP[b] 50 mg, 100 mg, 200 mg, 400 mg or Placebo (Panel 1); CZP[b] 600 mg, 800 mg or Placebo (Panel 2)	Every 4 weeks sc	12 weeks	323
Phase III Placebo-Controlled					
CDP870-011	Double-blind, placebo-controlled, parallel-group study	CZP[c] 400 mg or Placebo	Every 4 weeks sc	24 weeks	220
CDP870-014	Double-blind, placebo-controlled, parallel-group study	CZP[c] 400 mg or Placebo +MTX	Every 4 weeks sc	24 weeks	243
CDP870-027	Double-blind, placebo-controlled, parallel-group study	CZP[c] 400 mg, 200[d] mg or Placebo + MTX	Every 2 weeks sc	52 weeks	980
CDP870-050	Double-blind, placebo-controlled, parallel-group study	CZP[c] 400 mg, 200[d] mg or Placebo + MTX	Every 2 weeks sc	24 weeks	619
Long Term Follow-up					
CDP870-004	Open-label, extension study to CDP870-004	CZP[b] 200 mg then 400 mg (Panel 1) CZP 400[b] mg (Panel 2)	Every 4 weeks sc	104 weeks	298
CDP870-015	Open-label, extension study to CDP870-011 and CDP870-014	CZP[c] 400 mg +/- MTX	Every 4 weeks sc	Ongoing	402
CDP870-028	Open-label, extension study to CDP870-027	CZP[c] 400 mg + MTX	Every 2 weeks sc	Ongoing	846
CDP870-051	Open-label, extension study to CDP870-050	CZP[c] 400 mg +MTX	Every 2 weeks sc	Ongoing	567

Table 5 Four Phase 3 Trials supporting CZP in RA

Summary of Phase 3 CIMZIA in RA Studies				
	Study CZP 027	Study CZP 050	Study CZP 011	Study CZP 014
Study Design	MC, DB, PC, PG, lyophilized, MTX	MC, DB, PC, PG liquid, MTX	MC, DB, PC lyophilized	MC, DB, PC, PG lyophilized, MTX
Duration	52-weeks	24-weeks	24-weeks	24-weeks
Patient Population	Active RA, partial responders to MTX	Active RA, incomplete response to MTX	Active RA, failed at least 1 DMARD	Active RA, partial responders to MTX
Treatment	CZP 400 mg, 200 mg or PBO; q 2-weekly, sc; Loading dose CZP 400 mg at week 0, 2 and 4	CZP 400 mg, 200 mg or or PBO; q 2-weekly, sc; Loading dose CZP 400 mg at week 0, 2 and 4	CZP 400 mg or PBO, q 4 weeks, sc;	CZP 400 mg or PBO, q 4 weeks, sc;
Randomization Ratio	2:2:1 randomization	2:2:1 randomization	1:1 randomization	1:1 randomization
Total Randomized Pts.	N=992	N = 253	N = 220	N = 233
Escape to OL Study	If failed ACR20 repsonse at week 12, option to enter **OL Study CZP 028** at week 16.	If failed ACR20 repsonse at week 12, option to enter **OL Study CZP 051** at week 16.	If completed at week 12, eligible to enter **Study 015**	If completed at week 12, eligible to enter **Study 015**
Primary Endpoint at 24 Weeks	ACR20 Response	ACR20 Response	ACR20 Response	ACR20 Response
Co-Primary Endpoint 52 Weeks	Inhibition of Progression of Structural Damage			
Secondary Endpoints	26	17	16	11

5.2 Review Strategy

This efficacy and safety review is focused on four Phase 3 clinical trials (Study 027, 050, 014 and 011). Study 011 and 014 serve as supportive clinical trials to the two larger Phase 3 trials which explore dose-finding and radiographic efficacy in addition to the primary efficacy analyses.

5.3 Discussion of Individual Studies

Study CDP870-027 (Study 027)

Title - 027
A Phase 3 multicenter, double-blind, placebo-controlled, parallel group 52-week study to assess the efficacy and safety of 2 dose regimens of lyophilized CDP870 given subcutaneously as additional medication to methotrexate in the treatment of the signs and symptoms and preventing structural damage in patients with active rheumatoid arthritis who have an incomplete response to methotrexate. (Study period 18Feb-2005 to 12Sept-2006)

Primary Objectives -027
To assess the efficacy of 2 dose regimens of CZP in combination with MTX compared to MTX alone in the:
1. Treatment of signs and symptoms in patients with active RA, and
2. Prevention (inhibition of progression) of structural damage in patients with RA.

Secondary Objectives - 027
To assess the 2 dose regimens of CZP in combination with MTX compared to MTX alone in the:
1. Safety and tolerability in patients with active RA;
2. Major clinical response in patients with active RA;
3. Physical function in patients with active RA;
4. Health Outcome Measures (Health-Related Quality of Life [HRQOL], tiredness [fatigue], productivity) in patients with active RA
5. Pharmacokinetic (PK) profile and immunogenicity (anti-CZP antibodies profile) of 2 dose regimens of CZP in combination with MTX.

Study Design - 027
As shown in **Figure 2**, this was a double-blind, randomized, multicenter, placebo-controlled, parallel-group study which assessed the efficacy and safety of 2 dose regimens of lyophilized CZP administered subcutaneously (sc) in combination with MTX compared to MTX alone in the treatment of signs and symptoms and inhibition of the progression of structural damage in patients with active RA.

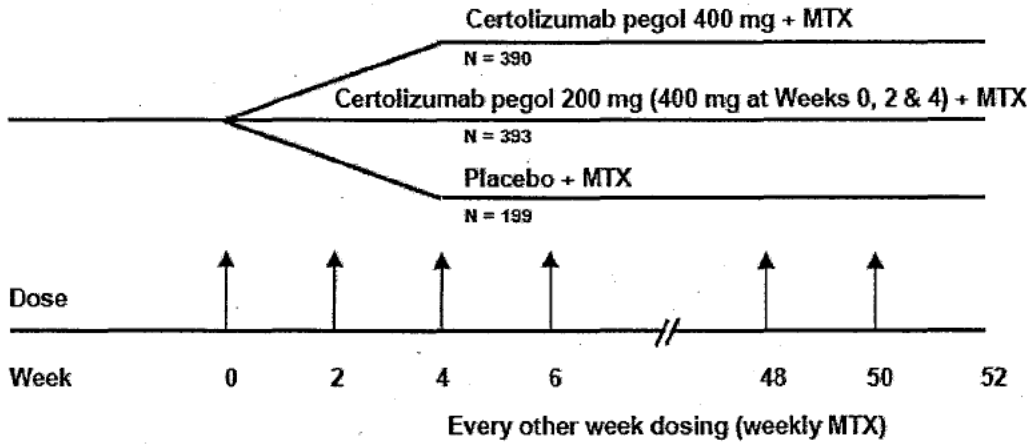
Study Conduct - 027
Study 027 consisted of a Screening visit, a 52-week Treatment period, and a 12-week Follow-up visit. Eligible patients were randomized to 1 of the following 3 study treatments in a 2:2:1 ratio:

1) CZP 200 mg q2w; 2) CZP 400 mg q2w; and 3) Placebo q2w (0.9% preservative free saline solution).

All patients continued their treatment on MTX with or without folic acid at the same dose as at entry (unless there was a need to reduce the dose for reasons of toxicity). Patients were assessed for safety and efficacy, including physical function and disability, rheumatoid arthritis pain, disease activity, HRQOL, tiredness (fatigue), productivity within and outside the home, and assessed for PK and immunogenicity variables throughout the study.

Patients who failed to achieve an ACR20 response at Week 12 (confirmed at the Week 14 visit) were designated as treatment failures and withdrawn. These patients and patients who completed the study at Week 52 were offered the choice at Week 16 of entering Study 028, an open-label long-term follow-up study. All patients had a Follow-up visit 12 weeks after their last dose of CZP/PBO unless they continued into the open-label Study 028.

Figure 2. Schematic Diagram of Study 027 Sponsor figure 9:1, page 40 of 8823



Study Population and Sample Size - 027

Sample size clculations allowed for an approximate screen failure rate of 25% between Screening and Baseline. Sample size was determined on the basis of anticipated differences between active CZP and PBO with regard to the 2 co-primary efficacy endpoints. For the sample size calculation for the first co-primary endpoint, the percentage of patients with an ACR-20 response at Week 24, a PBO rate of 30% was assumed and a difference between active CZP and PBO of 20% was considered clinically relevant. There were 2 active treatment comparisons to PBO for this endpoint; therefore, to preserve the overall Type I error rate at α=0.05, a significance level of 0.025 was used in the sample size calculation and subsequent statistical tests. In order to detect a difference of 20% (e.g., 30% PBO, 50% active CZP), at a 2-sided significance level of 2.5% in a 1:2:2 ratio with 90% power, a total of 590 patients were required (118 on placebo and 236 on each active arm).

For the modified total sharp score (mTSS), a sample size of 190 for placebo, and 380 for each active CZP group was sufficient to detect differences larger than 2.2 in the mean change from Baseline in the mTSS between an active and control group with at least 90% power (and

assuming a standard deviation of 7 points). The sample size was based on the larger of the 2 estimates so as to control the Type II error. A total of 950 patients were to be randomized.

Inclusion Criteria - 027

Patients had to meet all of the following criteria to qualify for study participation:

1. ≥18 years at the Screening visit.
2. A clear chest X-ray within 3 months prior to the Baseline visit.
3. If female, was either postmenopausal for at least 1 year, surgically incapable of child bearing, or effectively practicing an acceptable method of contraception (oral or parenteral hormonal contraceptives; intrauterine device; barrier and spermicidal). Patients had to agree to continue to use adequate contraception during the study and for 12 weeks after the last dose of CZP.
4. Had a diagnosis of adult-onset RA (of at least 6 months duration but not longer than 15 years prior to Screening), as defined by the 1987 ACR classification criteria.
5. Had active RA disease at Screening and Baseline defined as the following:
    - ≥9 tender joints
    - ≥9 swollen joints
    - And at least 1 of the following:
    - ESR ≥30 mm/h or
    - C-reactive protein (CRP) >15 mg/L.
6. Received treatment with MTX (with or without folic acid) for at least 6 months prior to the Baseline visit. The dose of MTX had to have been stable for at least 2 months prior to the Baseline visit. The minimum dose of MTX had to be equivalent to 10 mg weekly.
7. Willing to return at Week 52 for X-rays of the hands and feet even if the patient was no longer receiving study treatment but had not withdrawn informed consent.
8. Able to understand the information provided to them and provide written informed consent.

Exclusion Criteria - 027

Patients who met any of the following criteria were excluded from study participation:

1. Had a diagnosis of any other inflammatory arthritis (e.g., psoriatic arthritis or ankylosing spondylitis).
2. Had a secondary, non-inflammatory type of arthritis (e.g., osteoarthritis or fibromyalgia) that in the Investigator's opinion was symptomatic enough to interfere with evaluation of the effect of CZP on the patient's primary diagnosis of RA.
3. Had a history of an infected joint prosthesis at any time with prosthesis still *in situ*.
4. Any of the concomitant medication exclusion criteria listed in **Table 6**.

Table 6. Exclusion Based on Use of Concomitant Medications – Study 027

Drug class	Dose	Exclusion Criteria
Analgesics	Any dose	In the 24 hours prior to the Baseline arthritis assessment
NSAIDs/COX-2 inhibitors	Any dose regimen	Any change in dose regimen in the 14 days prior to Baseline Arthritis Assessment.
Oral corticosteroids	Maximum dose allowed not greater than 10 mg prednisone (or equivalent) per day	Any change in dose in the 28 days prior to the Baseline arthritis assessment.
IM/IV/IA corticosteroids	Any dose	In the 28 days prior to the Baseline arthritis assessment
IA hyaluronic acid	Any dose	In the 28 days prior to the Baseline arthritis assessment
DMARDs – sulfasalazine, azathioprine, cyclosporin, hydroxychloroquine, chloroquine, penicillamine, gold, cyclophosphamide.	Any dose	In the 28 days prior to the Baseline arthritis assessment
DMARDs – leflunomide	Any dose	In the 6 months prior to the Baseline arthritis assessment unless a cholestyramine washout had been performed (according to local guidelines), in which case 28 days prior to the Baseline arthritis assessment was acceptable.

5. Received any experimental non-biological therapy for RA, within or outside a clinical study in the 3 months prior to Baseline.
6. Received any biological therapy for RA within 6 months prior to Baseline, except for etanercept and anakinra where 3 months prior to Baseline was acceptable.
7. Had previous treatment with a biological therapy for RA that resulted in a severe hyper-sensitivity reaction or an anaphylactic reaction. Patients who previously had not responded to treatment with an anti-TNF drug were also excluded.
8. Were lactating and/or pregnant.
9. If female of childbearing potential, was not practicing effective birth control. All female patients had to have a negative serum pregnancy test before study entry and a negative urine pregnancy test immediately before every CZP administration.
10. Had a history of chronic infection, recent serious or life-threatening infection (within 6 months, including herpes zoster), or any current sign or symptom that may have indicated an infection (e.g., fever, cough).
11. Had a history of tuberculosis (TB), or positive chest X-ray for TB or positive (defined as positive induration per local medical practice) purified protein derivatives (PPD) skin test. Patients with a positive PPD skin test associated with previous vaccination where there was no clinical or radiographic suspicion of TB could have been enrolled at the discretion of the Investigator. Consideration was given to the fact that a positive PPD skin test with prior vaccination dose did not exclude latent TB.
12. Had a history of a lymphoproliferative disorder including lymphoma or signs and symptoms suggestive of lymphoproliferative disease at any time.
13. Were at a high risk of infection in the Investigator's opinion (e.g., patients with leg ulcers, indwelling urinary catheter, and persistent or recurrent chest infections or permanently bed ridden or wheelchair bound).
14. Had a known positive hepatitis B surface antigen test and/or hepatitis C antibody test result.

15. Received any vaccination (live or attenuated) within 8 weeks prior to Baseline, with the exception of Influenza and Pneumococcal vaccines.
16. Had active malignancy of any type or a history of malignancy (except basal cell carcinoma of the skin that had been excised prior to study start).
17. Had a history of blood dyscrasias.
18. Had current or recent history of severe, progressive, and/or uncontrolled renal, hepatic, hematological, GI, endocrine, pulmonary, cardiac, neurological, or cerebral disease.
19. Had known human immunodeficiency virus infection.
20. Had New York Heart Association 1964 class III-IV congestive heart failure 1964.
21. Had a history of, or suspected, demyelinating disease of the central nervous system (e.g., multiple sclerosis or optic neuritis).
22. Had a history of an adverse reaction to PEG or a protein medicinal product.
23. Had any other condition, which in the Investigator's judgment made the patient unsuitable for inclusion in the study.

Removal of Patients from Study 027
Patients were free to withdraw from the Study 027 at any time, without prejudice to their continued care. The investigator was to withdraw a patient from the study, if, in their opinion the patient's clinical condition warranted their withdrawal; the patient repeatedly failed to comply with the protocol; if other safety issues arose during the course of the study; the patient was in need of additional concomitant medication to that permitted by the protocol and or the patient had a positive pregnancy test. Similarly, the sponsor or contract research organization (CRO) in conjunction with the sponsor reserved the right to discontinue an enrolled patient for reasons listed above.

Treatment - 027
Patients were randomized to 1 of 3 study treatments in a 2:2:1 ratio:
1. CZP 200 mg q2w (given as 2 sc injections: 1 injection of CZP 200 mg and 1 injection of placebo) following an initial regimen of CZP 400 mg at Baseline, Week 2 and Week 4 (administered as 2 sc injections of CZP 200 mg).
2. CZP 400 mg q2w (given as 2 sc injections of CZP 200 mg).
3. PBO (0.9% preservative free saline solution) q2w, given as 2 sc injections.

Prior and Concomitant Medications - 027
Patients continued their treatment on MTX, with or without folic acid, at the same dose and route of administration as at entry (unless there was a need to reduce the dose for reasons of toxicity). **Table 7** lists the criteria for RA concomitant medications allowed during the study.

Table 7. RA Medications Allowed During Study 027

Drug class	Dose	Criteria
Oral corticosteroids	Not more than 10 mg prednisone (or equivalent) per day	The dose of corticosteroids may have been reduced according to local guidelines for reducing corticosteroids.
NSAIDs/COX-2 inhibitors	Any dose regimen	Changes, if needed, must not have been made in the 14 days prior to the arthritis assessments.
Analgesics	Any dosage regimen	There was no restriction on the use of analgesics but the patient could not take them in the 24 hours prior to the arthritis assessments.
IA/IM injections of corticosteroids	Not more than 80 mg methylprednisolone per injection (or equivalent).	One corticosteroid injection was allowed, if necessary, in the time period between Baseline and the Week 8 assessment. No further injections were allowed until after Week 24. No more than 2 injections were allowed in the time period between the Week 24 and Week 44 assessments, and no injections were allowed between the Week 44 and Week 52 visits.

The following concomitant medications were not permitted:
1. Any DMARD other than MTX;
2. Biological RA disease-modifying drugs whether licensed/approved or unlicensed/not approved;
3. Unlicensed non-biological RA disease-modifying drugs; and
4. IV corticosteroids.

Schedule of Visits and Events - 027
The schedule of study visits and events is listed in the following three **Tables 8** and **9.**

Table 8. Schedule of Visits and Events - Study 027

Activity	Screen[a]	BL	Weeks															
			1	2	4	5	6	8	9	10	12	14	16	18	20	22	24	26	Cont'd
IC, demographics, med history (including RA), rheumatoid factor, PPD test	X																		
Inclusion/exclusion criteria	X	X																	
Pregnancy testing	X	X		X	X		X	X		X	X	X	X	X	X	X	X	X	
CZP or placebo dosing		X		X	X		X	X		X	X	X	X	X	X	X	X	X	
Efficacy/Health Outcome/MRI Assessments																			
Radiographs of hands and feet		X[b]															X		
Patient[c,e] and Investigator[d,e] arthritis assessments	X	X	X	X	X		X	X		X	X	X	X		X		X		
CRP and ESR	X	X	X	X	X		X	X		X	X	X	X		X		X		
SF-36 and EQ-5D[e,g]		X									X						X		
WPS and HCRU		X			X			X			X		X		X		X		
FAS		X	X	X	X	X	X	X	X	X	X		X		X		X		
MRI assessment[f]		X[b]									X						X		
Safety Assessments																			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology/biochem/urine	X	X	X	X	X		X	X		X	X	X	X		X		X		
Autoantibodies		X															X		
Vital signs[g]	X	X		X	X		X	X		X	X	X	X	X	X	X	X	X	
Physical examination[h]	X										X						X		
Chest X-ray[y]	X																		
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK/ Immunogenicity Assessments																			
CZP concentration and anti-CZP antibodies		X	X	X	X	X	X	X	X	X	X			X			X		

Table 9 (Continued, Study 027)

Activity	Weeks													12-Week Follow-up
	28	30	32	34	36	38	40	42	44	46	48	50	52 (completion or withdrawal)	
IC, demographics, med history (including RA), rheumatoid factor, PPD test														
Inclusion/Exclusion														
Pregnancy testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CZP or placebo dosing	X	X	X	X	X	X	X	X	X	X	X	X		
Efficacy/Health Outcome/MRI Assessments														
Radiographs of hands and feet													X	
Patient[c] and Investigator[d] arthritis assessments	X		X		X		X		X		X		X	
CRP and ESR	X		X		X		X		X		X		X	X
SF-36 and EQ-5D[e]					X						X		X	
WPS and HCRU	X		X		X		X		X		X		X	
FAS	X		X		X		X		X		X		X	
MRI assessment[f]													X	
Safety Assessments														
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology/biochem/urine	X		X		X		X		X		X		X	X
Autoantibodies													X	X
Physical examination[a,i]					X								X	X
Chest X-ray[j]													X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Activity	Weeks													12-Week Follow-up
	28	30	32	34	36	38	40	42	44	46	48	50	52 (completion or withdrawal)	
PK/ Immunogenicity Assessments														
CZP concentration and anti-CZP antibodies		X			X			X			X		X	X

[a] 28-day Screening period.
[b] Taken prior to first dosing.
[c] HAQ-DI; Patient's Assessment of Arthritis Pain - VAS; Patient's Global Assessment of Disease Activity - VAS; duration of morning stiffness.
[d] Swollen joint and tender joint count; Physician's Global Assessment of Disease Activity – VAS.
[e] In addition, assessments were generally captured every 4 weeks following Week 24 instead of every 12 weeks as planned.
[f] Subset of patients (approximately 50).
[g] At each dosing visit, vital signs (systolic and diastolic blood pressure, respiration rate, temperature, and pulse rate) were taken within 15 minutes prior to dosing and again at 30 minutes post-dose.
[h] Included assessments of weight at Screening and Week 52.
[i] Within 3 months prior to Baseline visit.

Co-Primary Efficacy Endpoints - 027

- ACR-20 Response at Week 24ACR-20 Response at Week 24
- Modified Total sharp Score (mTSS) at Week 52

Treatment of Signs and Symptoms:

- ACR-20/50/70 response;

  The ACR20/50/70 response: the assessments were based on a ≥20/50/70% improvement in the number of tender joints, swollen joints, and in 3 of the 5 core set measures (Patient's and Physician's Global Assessments of Disease Activity - VAS, Patient's Assessment of Arthritis Pain - VAS, CRP, and physical function based on the HAQ-DI. The ACR-20/50/70 was not calculated at Week 16.

- Major clinical response, defined as ACR-70 response at any 2 time-points 24 weeks apart during the study and at all assessments in between;
- Sustained response, defined as ACR-20 responders at both Weeks 24 and 52;
- Number of tender joints;
- Number of swollen joints;

Assessment of joint tenderness and swelling: A total of 68 joints were examined for tenderness, including joints in the upper body (6), upper extremity (34), and lower extremity (28). An assessment for swelling was made on 66 joints of the 68 joints evaluated for tenderness; the hip joints were excluded. Swelling and tenderness were graded on a 4-point scale.

- Health Assessment Questionnaire - Disability Index (HAQ–DI);

  (HAQ-DI) is a patient reported questionnaire that provides an assessment of the impact of the disease and its treatment on physical function and disability.
- Patient's Assessment of Arthritis Pain - Visual Analogue Scale (VAS);
- Patient's Global Assessment of Disease Activity - VAS;
- Physician's Global Assessment of Disease Activity - VAS;
- CRP; and
- Duration of morning stiffness.

  Defined as the time (hours) elapsed between the time of usual awakening (even if not in the morning) and the time the patient was as limber as he/she would be during a day involving typical activities.

Inhibition of Progression of Structural Damage:

- mTSS;
- Joint erosion score; and
- Joint space narrowing score.

  The inhibition of the progression of structural damage was assessed with the radiographs. The mTSS, erosion score, and joint space narrowing score were used to assess the degree of structural damage. Radiographs of the hands and feet were taken to assess disease progression. A single posterior-anterior view of each hand and a single dorso-plantar view of each foot were taken prior to first dose of investigational product at Baseline and at Weeks 24 and 52/Withdrawal visit. Repeat radiographs up to 42 days after Baseline were assessed using the van der Heijde modified Total Sharp Score (mTSS). This reading was conducted centrally and independently by 2 of 3 experienced readers who were blinded to the treatment arm and chronologic order.

Physical Function and Disability:

- HAQ-DI;
- Short Form 36-item Health Survey, Physical Component Summary (PCS); and
- SF-36 Physical Functioning Domain.

Health-Related Quality of Life:

- SF-36 Physical and Mental Component Summaries (PCS and MCS) and domains.

  HRQoL was assessed using the Short Form 36-item Health Survey (SF-36). The SF-36 is a generic instrument that assesses 8 domains, namely physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The 8 domains are summarized in 2 component summaries, the PCS and the MCS scores, which are calculated based on the 8 domain scores according to Ware, 2001. A linear T-score transformation method is used so that both PCS and MCS have a mean of 50 and a standard deviation of 10 in the general U.S. population. This transformation is in contrast

to the 0-100 scoring used for the eight domains (higher scores indicating better HRQOL). The SF-36 was assessed at Baseline, Weeks 12, 24, 28, 32, 36, 40, 44, 48, and 52/Withdrawal visit.

Tiredness:

- Fatigue Assessment Scale (FAS);

  Patients were asked the following question: "Please rate your fatigue (weariness, tiredness) during the past week on a scale of 0-10" where 0 is "No fatigue" and 10 is "Fatigue as bad as you can imagine". The FAS was assessed at Baseline, Weeks 1, 2, 4, 5, 6, 8, 9, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52/Withdrawal visit.
- SF-36 Vitality domain.

  The Vitality domain includes four questions that asks patients to rate their level of tiredness ("tired", "worn-out") and energy ("full of pep", "energy") on a six-point scale.

Productivity:

- Work Productivity Survey (WPS)

  The WPS is a 9-question instrument used to assess the impact of arthritis on productivity within and outside the home during the preceding 4 weeks. One of the WPS questions concerns the employment status, 3 relate to work productivity outside the home and 5 ask about household work and daily activities. The WPS was assessed at Baseline, Week 4, then every 4 weeks thereafter up to the Study Completion/Withdrawal visit.

Additional Efficacy Measures:

- Disease Activity Score (28) Erythrocyte Sedimentation Rate [DAS28(ESR)];

  The disease activity score (DAS)28 [erythrocyte sedimentation rate (ESR)]: calculated using the tender and swollen joint count (carried out on 28 joints), the ESR (mm/hour) and the Patient's Global Assessment of Disease Activity - VAS.
- DAS remission, defined as a DAS28(ESR) score <2.6. It is important to note that FDA does not accept DAS remission as adequate to define remission as some patients meeting DAS remission criteria still have active disease.
- European League against Rheumatism (EULAR);

  EULAR response criteria: The DAS-based EULAR response criteria were developed to measure individual response in clinical trials. The EULAR response criteria classify individual patients as non-, moderate, or good responders, dependent on the extent of change and the level of disease activity reached as described in **Table 10.**

Table 10. EULAR Response Criteria – 027

	DAS28(ESR) Improvement from Baseline		
Present DAS28(ESR)	>1.2	0.6 to 1.2	<0.6
<3.2	Good response	Moderate response	No response
3.2 to 5.1	Moderate response		
> 5.1	Moderate response	No response	No response

- ESR;

• Changes in RA concomitant medication;
• Time to withdrawal due to lack of efficacy or adverse events (AEs) reflecting significant worsening of RA;
• EuroQol-5D (EQ–5D) Health State Evaluation (Europe only);

EQ-5D is composed of a 5-item health-status measure (mobility, self-care, usual activities, pain discomfort, and anxiety/depression) and a visual analogue scale (VAS). Each of the 5 health states is divided into 3 levels: no problem, some or moderate problems, and extreme problems and is scored as 1, 2, and 3, respectively. The EQ-5D VAS records the respondent's self-rated health status on a vertical 20 cm scale, 0 to 100 graduated (0=worst imaginable health status, 100=best imaginable health status). The EQ-5D was assessed at Baseline, Weeks 12, 24, 28, 32, 36, 40, 44, 48, and 52/Withdrawal visit.

• Healthcare Resource Utilization (HCRU) Questionnaire

HCRU is a study-specific questionnaire developed to capture data regarding resource utilization during the study, such as additional physician outpatient visits, hospitalizations, medical procedures, and home care visits. The HCRU was assessed at Baseline, Week 4, followed by every 4 weeks thereafter up to the Study Completion /Withdrawal Visit.

Pharmacokinetic/ Immunogenicity Variables - 027
• Plasma concentrations of CZP; and
• Plasma concentrations of anti-CZP antibodies.

Safety - 027
Safety variables included AEs, extent of exposure, laboratory values (hematology, biochemistry, urinalysis and auto-antibodies), vital signs, urine pregnancy testing, physical examination, body mass index, concomitant medications, and chest X-ray. A serious AE (SAE) was any untoward medical occurrence that at any dose: 1) resulted in death; 2) was life-threatening; 3) required inpatient hospitalization or prolongation of existing hospitalization; 4) resulted in persistent or significant disability/incapacity; 5) was a congenital anomaly or birth defect; 6) was an infection that required treatment with parenteral antibiotics; 7) important medical events, which based on medical or scientific judgment, may have jeopardized the patient, or may have required medical or surgical intervention to prevent any of the above.

Patients were monitored for AEs, including SAEs, from Screening through the follow-up visit 12 weeks after last dose. Details (duration, intensity, relationship to investigational product, action taken, outcome, and seriousness) were recorded on the case report form (CRF).

Other Investigations - 027
Magnetic resonance imaging (MRI) assessments of patients' hands and feet were performed at Baseline and Weeks 12, 24, and 52/Withdrawal visit, for a subgroup of patients (approximately 50). All patients at sites with adequate MRI facilities were to have MRI assessments until approximately 50 patients in the study have undergone these assessments. Measurements from the MRI scans were for exploratory purposes only and made by a central reader. Analysis of

MRI data will be conducted at a later stage and reported separately. These imaging readings have not yet been completed, and will be reported upon separately.

Statistical and Analytical Methods - 027

Study Populations

The Intent-to-Treat (ITT) population consisted of all randomized patients. In the case of dosing administration error, analyses on the ITT Population were conducted according to randomized treatment. This was the primary efficacy population.

The per-protocol (PP) populations were a subset of the ITT population, consisting of those patients who had no major protocol deviations affecting either primary efficacy variable or relating to the integrity of the study conduct, as confirmed during a pre-analysis review prior to unblinding of the data. Major protocol deviations included inclusion and exclusion criteria deviations, study medication compliance deviations, study visit compliance deviations, and receipt of a prohibited concomitant medication.

Post-Baseline deviations did not necessarily lead to exclusion of a patient from PP analyses but may have led to exclusion of data. The date from which a patient was excluded was confirmed during the pre-analysis meeting, in addition to the classification of patients to patient populations. These PP populations were used for sensitivity analyses on the primary endpoints only and for summary statistics of the demographic characteristics at Baseline. The 2 PP populations were PP (Signs and Symptoms) and PP (Structural Damage).

The safety population consisted of all patients who received at least 1 injection of investigational product. In the case of dosing administration error, analyses on the safety population were conducted according to actual treatment received.

Efficacy and Safety Analyses

As explained by the sponsor, for the primary analysis of ACR20 response at Week 24, treatment comparisons versus PBO for the 2 CZP dose groups were performed using logistic regression, with factors for treatment and region. The treatment effect was estimated using the odds ratio and corresponding 97.5% confidence interval (CI) obtained by fitting this model. Several sensitivity analyses were also performed. For change from Baseline in the mTSS, treatment comparisons versus PBO for the 2 CZP dose groups were performed using an analysis of covariance (ANCOVA) model on the ranks, with treatment and region as factors and rank Baseline mTSS as covariate. The treatment effect was estimated by Hodges-Lehmann point estimate of shift and 97.5% exact CI. The study was considered successful for the treatment of signs and symptoms primary objective if at least 1 of the 2 dose comparisons was statistically significant for the ACR20 responder endpoint. It was also declared successful for the inhibition of progression of structural damage objective if, given that the ACR20 endpoint was significant, the mTSS primary endpoint was also statistically significant for the same dose comparison. Analyses of the secondary and exploratory efficacy parameters were similar to those employed for the primary efficacy analyses. See Section 6.1 Efficacy Results for the Individual Study Conduct, Study 027.

Protocol Violations – 027

Signs and Symptoms

In the PP (Signs and Symptoms) population, 42 patients (4%) were excluded: the CZP 200 mg + MTX group had the highest number of patients with at least 1 Per Protocol Total (PPT) deviation 23 (6%). The CZP 400 mg + MTX group had 12 (3%) patients with deviations, and the PBO + MTX group had 7 (4%) patients. Patients with at least 1 PPT deviation were excluded from the PP Population. The most common protocol deviation was "ineligibility in general," which occurred in 5 (3%) patients in the PBO + MTX group, 11 (3%) patients in the CZP 200 mg + MTX group, and 6 (2%) patients in the CZP 400 mg + MTX group.

Structural Damage

In the PP (Structural Damage) population, 43 patients (4%) overall were excluded: the CZP 200 mg + MTX group had the highest number of patients with at least 1 PPT deviation (22, 6%). The CZP 400 mg + MTX group had 13 (3%) patients with deviations, and the PBO + MTX group had 8 (4%) patients. The most common protocol deviation was "ineligibility in general," which occurred in 5 (3%) patients in the PBO + MTX group, 11 (3%) patients in the CZP 200 mg + MTX group, and 6 (2%) patients in the CZP 400 mg + MTX group. The more common deviations included changes in NSAID dosing within 14 days of an arthritis assessment, changes in MTX dosing, Baseline chest X-rays not being performed within window and withdrawal X-ray of hands and feet not being performed. As explained by the sponsor, despite their occurrence, the patients remained in the study; however, they were partially (on a defined date) excluded from the PP population analysis.

Patient # 052/002 and patient # 212/011 had their study treatment blind broken by the investigator.

- Patient # 052/002 was unblinded by the investigator due to an outcome of death resulting from an SAE of myocardial infarction.
- Although the specific cause for unblinding is unknown, Patient 212/011 was discontinued due to adverse events of lung infiltration and pleurisy.

Study CDP870-050 (Study - 050)

Title - 050

A Phase 3, multi-center, double-blind, placebo-controlled, parallel-group, 24-week study to assess the efficacy and safety of 2 dose regimens of liquid certolizumab pegol as additional medication to methotrexate in the treatment of signs and symptoms of rheumatoid arthritis and in prevention of joint damage in patients with active rheumatoid arthritis who have an incomplete response to methotrexate. (Study period: June 30, 2005 to September 19, 2006)

Primary Objectives - 050

1. The primary objective of the Study 050 was to compare the efficacy of 2 dose regimens of a liquid formulation of CZP in combination with MTX to MTX alone in the treatment of signs and symptoms in patients with active rheumatoid arthritis (RA).

Secondary Objectives - 050
The secondary objectives were to assess the 2 dose regimens of CZP in combination with MTX compared to MTX alone in terms of the:
1. Safety and tolerability in patients with active RA
2. Prevention of joint damage in patients with active RA
3. Physical function and disability in patients with active RA
4. Health Outcome Measures (Health-Related Quality of Life [HRQOL], tiredness [fatigue], productivity) in patients with active RA
5. Assessment of the pharmacokinetic (PK) profile and anti-CZP antibody profile of 2 dose regimens of liquid formulation CZP in combination with MTX.

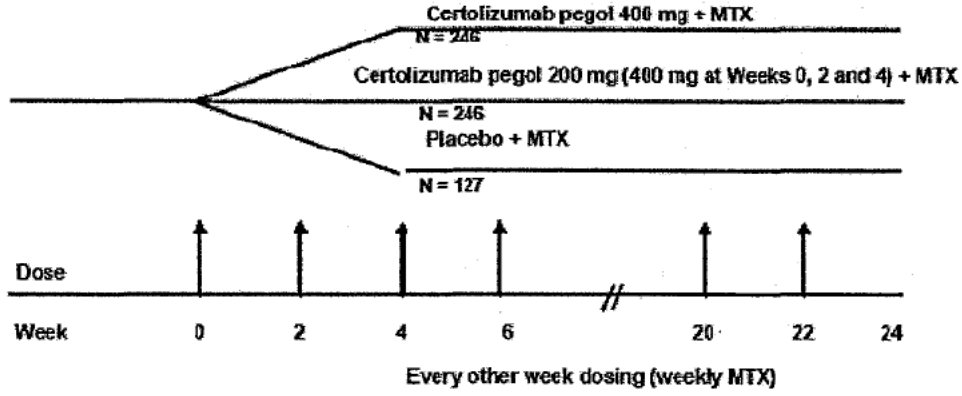
Study Design - 050
As shown in **Figure 3**, this was a double-blind, randomized, multicenter, placebo-controlled, parallel-group study which assessed the efficacy and safety of 2 dose regimens of liquid CZP administered subcutaneously (sc) in combination with background MTX compared to background MTX alone in the treatment of signs and symptoms in patients with active RA and an incomplete response to MTX.

Study Conduct - 050
Study 050 consisted of a Screening visit, a 24-week treatment period, and a 12-week Follow-up visit. Patients were randomized to 1 of the following 3 treatment groups in a 2:2:1 ratio:
1) CZP 200 mg q2w (given as 2 sc injections: 1 injection of CZP 200 mg and 1 injection of PBO) following an initial regimen of CZP 400 mg at Baseline, Week 2 and Week 4 (given as 2 sc injections of CZP 200 mg);
2) CZP 400 mg every 2 weeks (given as 2 sc injections of CZP 200 mg); and 3) PBO (0.9% preservative free saline solution) every 2 weeks (given as 2 sc injections). As with Study 027, patients continued MTX with or without folic acid at the same dose as at entry (unless there was a need to reduce the dose for toxicity).

Patients were assessed for safety and efficacy, including physical function, HRQOL, tiredness (fatigue), productivity, disease activity, arthritis pain, and PK/immunologic variables throughout Study 050.

In order to address ethical issues in regard to continuing patients on PBO past 16 weeks if there was no response, designated patients that failed to achieve an ACR20 response at Week 12, (confirmed at Week 14), were designated as treatment failures. After the Week 14 visit, these patients were withdrawn and offered the choice of entering the open-label extension Study 051 at Week 16. Patients had a Follow-up visit 12 weeks after their last dose of investigational product unless they continued into Study 051. Patients who entered Study 051 prior to completing all of the study visits were to have a Follow-up visit 24 weeks after their Study 050 Baseline visit. Fifteen patients were excluded from Study 050, Site # 104, Lithuania) due to fraud and misconduct. See Section 3.1 ETHICS AND GOOD CLINCIAL PRACTICES, Subsection 3.1 Submission Quality and Integrity.

Figure 3. Schematic Diagram of Study 050 (Sponsor figure 9:1, page 39 of 6142)



Study Population and Sample Size - 050

A total of 590 patients were planned for randomization. It was expected that ~790 patients would have been needed for Screening, allowing for a 25% screen failure rate between Screening and Baseline. The sample size was determined on the basis of anticipated differences between CZP and PBO in the percentage with an ACR20 response at Week24. Patients were randomized to the three groups as described earlier in this study description. To detect a difference of 20% (i.e., 30% PBO, 50% CZP) at a 2-sided significance level of 3% for a 1:2:2 ratio with 90% power, it was estimated that a total of 590 patients would be required (118 PBO and 236 CZP treatment group). To control the overall study–wise Type I error rate at 5%, a Closed Test procedure (Koch) was used to control for multiple comparisons across the secondary efficacy endpoints. Hypothesis testing was performed on the secondary variables at a 5% significance level, but only if the primary endpoint was significant at the 2.5% significance level. It should be noted that, with 236 patients in each active dose group, the study was estimated to have approximately 80% power at the 5% significance level to detect a difference in the ACR20 response of 13% between the 2 CZP treatment groups, given an expected response for CZP 200 mg every 2 weeks in the region of 60%.

Inclusion Criteria - 050

Patients had to meet all of the following criteria to qualify for Study 050 participation:

1. ≥18 years at the Screening visit.
2. A clear chest X-ray within 3 months prior to the Baseline visit.
3. Female patients of childbearing potential must have had a negative serum pregnancy test at Screening and negative urine testing immediately before every investigational product administration. Females must have been surgically sterile, postmenopausal for at least 2 years prior to Screening, must have undergone tubal ligation or be using an acceptable method of birth control for the duration of the study and for 12 weeks after the last dose of CZP. Oral contraceptives must have been stable for at least 28 days prior to the screening visit. Abstinence was not an acceptable method of contraception for the study.
4. A diagnosis of adult-onset RA (of at least 6 months duration but not longer than 15 years prior to Screening) as defined by the 1987 ACR classification criteria.

5. Active RA disease at Screening and Baseline as defined by:
   - ≥ 9 tender joints
   - ≥ 9 swollen joints
   - And fulfillment of 1 of the following 2 criteria:

   a. ≥ 30 mm/hour erythrocyte sedimentation rate (ESR) (Westergren), or
   b. C-reactive protein (CRP) >15 mg/L.

6. Received treatment with MTX (with or without folic acid) for at least 6 months prior to the Baseline visit. The dose of MTX had to have been stable for at least 2 months prior to the Baseline visit. The minimum dose of MTX had to be equivalent to 10 mg weekly.
7. Willing to attend Week 24 for X-ray of the hands and feet even if they were no longer receiving study treatment but had not withdrawn informed consent.
8. Able to understand the information provided to them and give written informed consent.

Exclusion Criteria - 050
Patients who met any of the following criteria were to be excluded from Study 050 participation:
1. Diagnosis of any other inflammatory arthritis (e.g., psoriatic arthritis or ankylosing spondylitis).
2. A secondary, non-inflammatory type of arthritis (e.g., osteoarthritis or fibromyalgia) that in the Investigator's opinion was symptomatic enough to interfere with evaluation of the effect of CZP on the patient's primary diagnosis of RA.
3. History of an infected joint prosthesis at any time with prosthesis still *in situ*.

Exclusions, Previous Clinical Trial and Previous Biologic Therapy - 050
1. Received any experimental non-biological therapy, within or outside a clinical trial in the 3 months prior to Baseline.
2. Received any biological therapy for RA within 6 months prior to Baseline, except for etanercept and anakinra, where 3 months prior to Baseline was acceptable.
3. Previous treatment with a biological therapy for RA that resulted in a severe hypersensitivity reaction or, an anaphylactic reaction. Patients who previously had not responded to treatment with an anti-TNF drug were also excluded.
4. Were lactating and/or pregnant, or planned to become pregnant during the trial or within 3 months following the last dose of investigation product.

Exclusions, Medical History - 050
1. If female of childbearing potential, was not practicing effective birth control. All female patients had to have a negative serum pregnancy test before study entry and a negative urine pregnancy test immediately before every CZP administration.
2. History of chronic infection, recent serious or life-threatening infection (within 6 months, including herpes zoster), or any current sign or symptom that may have indicated an infection (e.g., fever, cough).
3. History of tuberculosis (TB) or positive chest X-ray for TB or positive purified protein derivatives (PPD) skin test (defined as positive induration per local medical practice). Patients with a positive PPD skin test associated with previous vaccination where there was no clinical or radiographic suspicion of TB could have been enrolled at the discretion of the Investigator.

Consideration was given to the fact that a positive PPD skin test with prior vaccination dose did not exclude latent TB.
4. History of a lymphoproliferative disorder including lymphoma or signs and symptoms suggestive of lymphoproliferative disease at any time.
5. Were at a high risk of infection in the Investigator's opinion.
6. Known positive hepatitis B surface antigen test and/or hepatitis C antibody test result.
7. Received any vaccination (live or attenuated) within 8 weeks prior to Baseline. (Influenza and Pneumococcal vaccines were allowed).
8. Active malignancy of any type or a history of malignancy (except basal cell carcinoma of the skin that had been excised prior to study start).
9. History of blood dyscrasias.
10. Current or recent history of severe, progressive, and/or uncontrolled renal, hepatic, hematological, GI, endocrine, pulmonary, cardiac, neurological, or cerebral disease.
11. Known human immunodeficiency virus infection.
12. New York Heart Association 1964 class III-IV congestive heart failure.
13. History of, or suspected, demyelinating disease of the central nervous system (e.g., multiple sclerosis or optic neuritis).
14. History of an adverse reaction to PEG or a protein medicinal product.
15. Any other condition, which in the Investigator's judgment made the patient unsuitable for inclusion in the study.

Removal of Patients from Study - 050
This portion of the protocol is similar to that described for Study 027.

Treatment - 050
Patients were randomized to 1 of the following 3 treatment groups in a 2:2:1 ratio:
1. CZP 200 mg every 2 weeks (given as 2 sc injections: 1 injection of CZP 200 mg and 1 injection of placebo) following an initial loading regimen of CZP 400 mg at Baseline, Week 2 and Week 4 (given as 2 sc injections of CZP 200 mg).
2. CZP 400 mg every 2 weeks (given as 2 sc injections of CZP 200 mg).
3. Placebo (0.9% preservative free saline solution) every 2 weeks (given as 2 sc injections).

Investigational Product Formulation - 050
Earlier clinical studies of CZP used either a reconstituted lyophilized formulation (Study 011, 014 and 027) or a different liquid formulation (Study 004). Study 050 used a new liquid formulation, which was compared to the lyophilized formulation in a bioavailability study (Study 038).

Prior and Concomitant Medication - 050
Patients would be excluded who did not meet the concomitant medication criteria (**Table 11**).

Table 11. Prior and Concomitant Medication, Study 050

Drug class	Dose	Exclusion Criteria
Analgesics	Any dose	In the 24 hours prior to the Baseline arthritis assessment.
NSAIDs/COX-2 inhibitors	Any dose regimen	Any change in dose regimen in the 14 days prior to Baseline Arthritis Assessment.
Oral corticosteroids	Maximum dose allowed not greater than 10 mg prednisone (or equivalent) per day	Any change in dose in the 28 days prior to the Baseline arthritis assessment.
IM/IV/IA corticosteroids	Any dose	In the 28 days prior to the Baseline arthritis assessment.
IA hyaluronic acid	Any dose	In the 28 days prior to the Baseline arthritis assessment.
DMARDs – sulfasalazine, azathioprine, cyclosporin, hydroxychloroquine, chloroquine, penicillamine, gold, cyclophosphamide.	Any dose	In the 28 days prior to the Baseline arthritis assessment.
DMARDs – leflunomide	Any dose	In the 6 months prior to the Baseline arthritis assessment unless a cholestyramine washout had been performed (according to local guidelines); in which case, 28 days prior to the Baseline arthritis assessment was acceptable.

Study Schedule of Visits and Events - 050

Table 12 includes the schedule of study visits and events for Study – 050. Pharmacokinetic, pharmacodynamic and safety measurements are also listed in the flow chart.

Table 12. Schedule of Study Visits and Events - 050

Protocol Activity	Screening[a]	Baseline															
Week Number	–4 to –1	0	1	2	4	5	6	8	9	10	12	14	16	18	20	22	24/W	12WFU[b]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Inclusion/Exclusion	X	X																
Informed Consent	X																	
Demographic Data	X																	
RA History	X																	
Significant Past Medical History and Concomitant Diseases	X																	
Vital Signs[c]	X	X		X	X		X	X		X	X	X	X	X	X	X	X	X
Body Mass	X																X	
Hematology/Biochem/Urine[d]	X	X	X	X	X		X	X		X	X	X			X		X	X
Physical Examination	X										X						X	X
Rheumatoid Factor	X																	
Chest X–ray[e]	X																X	
PPD Skin Test	X																	
X–ray Hands and Feet[f]		X[g]															X	
Patient Arthritis Assessments[h]	X	X	X	X	X		X	X			X	X	X		X		X	
Investigator Arthritis Assessments[i]	X	X	X	X	X		X	X			X	X	X		X		X	
SF–36 Health Survey		X									X						X	
EQ–5D Health Evaluation (EU only)		X									X						X	
Fatigue Assessment Scale		X	X	X	X		X	X			X						X	
HCRU		X			X			X			X		X		X		X	
Work Productivity Survey		X			X			X			X		X		X		X	
Plasma for CZP concentration and anti–CZP antibodies		X	X	X	X	X	X	X	X		X						X	X
Plasma for Autoantibodies		X															X	X
Pregnancy Testing[j]	X	X		X	X		X	X		X	X	X	X	X	X	X	X	X

Continued, **Table 12.**

Protocol Activity	Screening[a]	Baseline															
Week Number	–4 to –1	0	1	2	4	5	6	8	9	10	12	14	16	18	20	22	24/W	12WFU[b]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CZP or Placebo Administration[c]		X		X	X		X	X		X	X	X	X	X	X	X		

[a] Screening period, 7 to 28 days prior to Baseline visit. Patients returned 48 to 72 hours after the Screening visit to have their PPD test assessed.
[b] Follow-up (FU) visit was performed 12 weeks after the last dose for patients who discontinued treatment early, or completed the study and did not enter the open-label follow-up study (CDP870-051).
[c] Pulse, systolic/diastolic blood pressure, temperature and respiration rate were within 15 minutes prior to dosing and repeated 20 to 40 minutes after dosing.
[d] Includes CRP and ESR.
[e] Within 3 months prior to Baseline visit.
[f] Patients were to have a follow-up X-ray performed 24 weeks after their Baseline visit. This included patients prematurely withdrawn from treatment and those who entered CDP7870-051.
[g] Taken prior to first dosing. A repeat X-ray was permitted within 14 days of the Baseline visit in the event the original Baseline X-ray was not evaluable
[h] HAQ-DI; Patient's Assessment of Arthritis Pain - VAS; Patient's Global Assessment of Disease Activity - VAS; Duration of morning stiffness
[i] Swollen joint and tender joint count; Physician's Global Assessment of Disease Activity - VAS
[j] Serum pregnancy test at the Screening visit and urine pregnancy tests at the Baseline visit, Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, (prior to dosing) and Week 24/Withdrawal visit and Follow-up visits.
[k] If a patient was >5 days late for a dosing visit, the investigational product was not administered. The next dose was given at the next scheduled visit. If a patient was >5 days late for >1 dosing visit, the site contacted the medical monitor for instructions on how to proceed

Primary Efficacy Endpoint – 050

- ACR-20 at Week 24 (Visit 17) was the primary efficacy variable.

Secondary Efficacy Endpoints – 050

Treatment of Signs and Symptoms

- ACR-20/50/70 response
- Number of tender joints
- Number of swollen joints
- HAQ–DI (Physical Function and Disability)
- Patient's Assessment of Arthritis Pain - VAS
- Patient's Global Assessment of Disease Activity - VAS
- Physician's Global Assessment of Disease Activity - VAS
- CRP
- Duration of morning stiffness

Inhibition of Structural Damage

- mTSS
- Joint erosion score
- Joint space narrowing score

Physical Function and Disability

- HAQ–DI
- Short-Form 36-item Health Survey (SF-36) Physical Component Summary
- SF-36 Physical Functioning domain

Health-Related Quality of Life

- SF-36 Physical and Mental Component Summaries and domains

Tiredness

- FAS

• SF-36 Vitality domain

Productivity
• Work Productivity Survey (WPS)

Additional Efficacy Measures
• Disease Activity Score [DAS28(ESR)]
• European League against Rheumatism (EULAR) Response
• ESR
• Changes in RA concomitant medication
• Time to withdrawal due to lack of efficacy or AEs reflecting significant worsening of RA
• EQ–5D Health State Evaluation (EU only)
• Healthcare Resource Utilization (HCRU) Questionnaire

Pharmacokinetic/ Immunogenicity Variables - 050
• Plasma concentrations of CZP
• Plasma concentrations of anti-CZP antibodies

Safety - 050
Safety variables included AEs, extent of exposure, laboratory values (hematology, biochemistry, urinalysis, and auto-antibodies), vital signs, urine pregnancy testing, physical examination, body mass index, concomitant medications, and chest X-ray. A serious AE (SAE) was any untoward medical occurrence that at any dose: 1) resulted in death; 2) was life-threatening; 3) required in-patient hospitalization or prolongation of existing hospitalization; 4) resulted in persistent or significant disability/incapacity, or 5) was a congenital anomaly or birth defect; 6) was an infection that required treatment with parenteral antibiotics; or 7) other important medical events which based on medical or scientific judgment may have jeopardized the patient, or may have required medical or surgical intervention to prevent any of the above.

Patients were monitored for AEs, including SAEs, after signature of the Informed Consent until the Follow-up visit 12 weeks after last dose. Details (duration, intensity, relationship to investigational product, action taken, outcome, and seriousness) were recorded on the CRF.

Statistical Methods - 050
Study Populations
The intent-to-treat (ITT) population consisted of all randomized patients. In the case of dosing administration error, analyses on the ITT population were conducted according to randomized treatment. This was the primary efficacy population.

The per-protocol (PP) population was a subset of the ITT population, consisting of those patients who had no major protocol deviations, as confirmed during a pre-analysis review prior to unblinding of the data. The PP population was used for sensitivity analyses on the primary endpoints only and for some background and demography tables (e.g., Demography, History of RA, RA Baseline Characteristics, PPD Skin Test Results, Summary of Past DMARD Medication for RA, Summary of past TNF inhibitor or other biological medication for RA, Summary of

Concurrent RA Medications at Baseline, Summary of Previous Medications, Summary of Concurrent Medications, Summary of Concomitant Medications, and Summary of Post-Treatment Medications).

The safety population consisted of all patients who took investigational product. In the case of dosing administration errors, analyses on the Safety population were conducted according to actual treatment received.

Efficacy and Safety Analyses

For the analysis of ACR20 response at Week 24, patients who withdrew for any reason or used rescue medication were considered as non–responders from that time-point onwards. Treatment comparisons versus PBO for the 2 CZP dose groups were performed using logistic regression with factors for treatment and region. The treatment effect was estimated using the odds ratio and corresponding 97.5% CI obtained by fitting this model. Several sensitivity analyses were also performed. The study was considered successful for the treatment of signs and symptoms objective if at least 1 of the 2 dose comparisons was statistically significant for the ACR-20 endpoint. The ACR20 responder rate at Week 24 was also analyzed for the PP population. This analysis was to be considered supportive of the primary efficacy analysis.

Analyses of the secondary and exploratory efficacy parameters were generally similar to those employed for the primary efficacy analyses. Adverse events (AEs) were classified according to the Medical Dictionary for Regulatory Activities (MedDRA). Incidence tables were used to summarize AEs. The proportion of patients with antibodies to CZP was summarized, as were shifts in autoantibody presence (anti-double-stranded DNA [anti–dsDNA] and antinuclear antibodies [ANA]).

Protocol Deviations and Violations - 050

Patients with at least 1 per-protocol total (PPT) deviation were excluded from the PP population. The CZP 200 mg + MTX group had the highest number of patients with at least 1 Per Protocol Total (PPT) deviation (15 patients, 6%). The CZP 400 mg + MTX group had 8 (3%) patients with deviations, and the PBO group had 2 (1.6%) patients.

Major Deviations

Only major deviations impacted the Study 050 analysis populations. As reported by the sponsor, for the 25 patients excluded from the PP population, there were a total of 55 protocol violations, comprising 25 minor and 30 major protocol violations. The most common protocol deviation was "ineligibility in general," which occurred in 1 (0.8%) patient in the PBO group, 8 (3%) patients in the CZP 200 mg + MTX group, and 6 (2%) patients in the CZP 400 mg + MTX group.

Overall, 80 (13%) patients had at least one partial deviation and were excluded from the relevant PP Population from the date of first partial deviation. Prohibited medication/treatment in the treatment period was the most common cause of partial exclusion from the PP population (9% of patients).

Study CDP870-014 (Study 014)

Title - 014
Efficacy and Safety of CDP870 400 mg Subcutaneously in Combination with Methotrexate Compared to Methotrexate Alone in the Treatment of the Signs and Symptoms of Patients with RA who are Partial Responders to Methotrexate (Study period October 23, 2002 to January 12, 2004)

Primary Objective - 014
The primary objective of this study was to compare the efficacy of CZP in combination with MTX to MTX alone in treating the signs and symptoms of patients with RA who are partial responders to MTX.

Secondary Objectives - 014
1. To evaluate the safety and tolerability of CZP in combination with MTX;
2. To characterize the effect of CZP in combination with MTX on health outcomes measures;
3. To characterize the immunogenic profile of CZP when it is used as combination therapy with MTX;
4. To determine systemic exposures of CZP.

Study Design - 014
Study 014 was a 24-week, multi-center, double-blind, randomized, placebo-controlled, parallel group study designed to compare the efficacy of CZP 400 mg sc q4w in combination with MTX (15 to 25 mg/week [doses as low as 10 mg were permitted if reduced due to toxicity) to MTX alone in treating the signs and symptoms of patients with RA who are partial responders to MTX.

Study Conduct - 014
It was planned that a minimum of 300 patients would be screened, and 250 patients (125 per treatment arm) would be randomized. Patients who completed Study 014 or who withdrew on or after the Week 12 visit were eligible to participate in the open-label safety Study 015, unless they were withdrawn from Study 014 due to non-compliance or a possibly study drug-related adverse event (AE).

Patients were required to visit the investigational site up to 14 occasions (depending on whether they completed the study: Screening, Baseline, Week 1, 2, 4, 8, 12, 16, 20, 21, 22, 24, Follow-up Visit 4, and 12 Weeks after Last Dose) for assessments and study procedures. Female subjects participating in Austria were additionally seen at 8 weeks after the last dose for a pregnancy test. If the patient did not participate in the open-label study or if the patient withdrew from Study 014 study before Week 12, follow-up visits occurred 4 and 12 weeks after the last dose of CZP 400 mg.

Study Population and Sample Size - 014
The sample size for Study 014 was based on the expected percent of responders to ACR20 criteria. It was anticipated that 30% of MTX alone patients and 50% of patients assigned to receive CZP + MTX treatment would achieve an ACR20 response at Week 24. A sample of 125

per treatment group would be sufficient to detect the above difference with an $\alpha = 0.05$ (two-sided test) and a power of 80%. It was planned to enroll 250 patients with projected retention of 243 patients for the efficacy modified intent-to-treat (mITT) analyses and projected retention of 243 patients for the safety analyses.

Patients 18 to 75 years of age, diagnosed with RA of at least 6 months duration as defined by the 1987 ACR, received MTX for at least 6 months, and on a stable dose of MTX between 15 and 25 mg/week for at least 8 weeks prior to the first dose of study medication (doses as low as 10 mg were permitted if reduced due to toxicity), who met all other inclusion/exclusion criteria, were considered eligible to enroll in Study 014.

Inclusion Criteria - 014

Patients who met the following inclusion criteria were eligible for enrollment into Study 014:

1. 18 to 75 years of age, inclusive;
2. If female and of childbearing potential, she agreed to participate in this study by providing written informed consent, had been using adequate contraception since last menses, was to use adequate contraception during the study and for 12 weeks after the study, was not lactating, and had a negative serum pregnancy test at Screening, and negative urine test on the day of receiving the first dose of study medication;
3. Had a diagnosis of adult-onset RA of at least 6 months duration as defined by the 1987 ACR classification criteria;
4. Had active disease at Screening and Baseline as defined by:
    - ≥ 9 tender joints
    - ≥ 9 swollen joints and fulfilled 1 of the following 3 criteria:
    - ≥ 45 minutes duration of morning stiffness,
    - ≥ 28 mm/hour ESR (Westergren), or
    - C-Reactive Protein (CRP) > 10 mg/L (> 1.0 mg/dL);
5. Had received MTX for at least 6 months and been on stable dose of MTX between 15 and 25 mg/week for at least 8 weeks prior to the first dose of study medication, and was expected to remain stable on this medication for the next 6 months. A MTX dose of 10 to 15 mg/week was acceptable in case a patient's dose had previously been reduced from 15 to 25 mg/week because of toxicity;
6. Had been on a stable dose of folic acid for at least 4 weeks prior to the first dose of study medication;
7. Had discontinued all other DMARD therapy (except MTX) for at least 28 days prior to first dose of study medication;
8. Had provided written informed consent before undergoing any study procedures.

Exclusion Criteria - 014

Patients could not enter the study if any of the following criteria applied:

1. Diagnosis of any other inflammatory arthritis (e.g., psoriatic arthritis or ankylosing spondylitis);
2. A secondary, non-inflammatory type of arthritis (e.g., osteoarthritis or fibromyalgia) that in the Investigator's opinion was symptomatic enough to interfere with evaluation of the effect of CZP on the patient's primary diagnosis of RA;

3. A history of chronic infection, recent serious or life threatening infection (within 6 months, including herpes zoster), or any current sign or symptom which indicated an infection (e.g., fever, cough);
4. History of tuberculosis or positive chest X-ray for tuberculosis or positive (defined as positive induration per local medical practice) purified protein derivative (PPD) skin test (Mantoux test). Patients with a positive PPD skin test who had received a Bacillus of Calmette and Guerin (BCG) vaccination and had a negative chest X ray for tuberculosis could have been enrolled;
5. A history of an infected joint prosthesis at any time with prosthesis still *in situ*;
6. Known human immunodeficiency virus (HIV) infection;
7. A positive hepatitis B surface antigen test and/or hepatitis C antibody test result during the Pretreatment Period;
8. Active malignancy of any type or a history of malignancy except basal cell carcinoma of the skin that had been excised prior to study start;
9. Current or recent history of severe, progressive, and/or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease;
10. The patient had New York Heart Association (NYHA) class III-IV congestive heart failure requiring medical treatment;
11. History of, or suspected, demyelinating disease of the central nervous system (e.g. multiple sclerosis or optic neuritis); Uncontrolled diabetes mellitus type I or type II as defined as hemoglobin A1c (HbA1c) $\geq$ 8.5%;
13. Patient was wheelchair bound or bedridden;
14. Persistently abnormal aspartate aminotransferase (AST) or alanine aminotransferase (ALT) results, i.e., greater than 1.5 times the upper limit of normal;
15. Hemoglobin levels < 9 mg/dl or hematocrit < 30%;
16. Total white blood cell (WBC) count of < 3.0 x 109/L (< 3000/mm3);
17. Platelet count < 100 x 109/L (< 100,000/mm3);
18. Serum creatinine greater than 1.5 times the upper limit of normal for the patient based on their age and sex;
19. Concurrent use of oral corticosteroids unless at a stabilized dose of $\leq$ 10 mg/day prednisone (or its equivalent) for 4 weeks prior to enrollment into the study and remained at that dose during the study. NSAIDs, COX-2 specific inhibitors must have been at a stabilized dose for 4 weeks prior to enrollment into the study and must have remained at that dose during the study;
20. Intra-articular, intramuscular, or IV corticosteroids in the 4 weeks preceding dosing;
21. Injection of hyaluronic acid in the 4 weeks prior to Baseline;
22. Use of analgesics within 4 days prior to Baseline assessments (paracetamol/ acetaminophen within 24 hours). Continuous treatment with aspirin < 325 mg/day when stable for at least 28 days prior to the first dose of study medication for non-arthritic reason was permitted;
23. Prior treatment with a TNF blocking agent including CZP;
24. A history of an adverse reaction to polyethylene glycol (PEG) or murine (mouse) derived product;
25. Receipt of any experimental, unregistered therapy or biological therapies for RA, within 6 months prior to study entry (Screening);
26. Any other condition which in the Investigator's judgment would have made the patient unsuitable for inclusion in the study.

Removal of Patients from Study - 014
Patients were free to withdraw from Study 014 at any time, without prejudice to their continued care. See Study 027, as the criteria of this protocol section are comparable.

Treatment - 014
Each patient received either CZP or PBO together with their ongoing dose of MTX. The investigational drug supplies, provided by Pharmacia/Pfizer, consisted of the following:

- CZP for injection 200 mg/vial: lyophilized solid in 5 mL glass vial;
- PBO for CZP: 70% weight-to-weight (w/w) sorbitol solution in 5 mL glass vial;
- MTX was supplied by local prescription.

Dose Selection - 014
Initial clinical data from Study 004 suggested that CZP 400 mg sc q4w had clinical activity in treating the signs and symptoms of RA and was well-tolerated. Study 004 was a multi-center, double-blind, placebo-controlled study that assessed the safety and efficacy of sc CZP doses of 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, and 800 mg vs PBO after 12 weeks (study drug administered at 0, 4, and 8 weeks).

Prior and Concomitant Medications - 014
The following medications were prohibited for the duration of the study:
1. Any experimental therapy or biological therapy;
2. Any Biological Response Modifier that blocked TNF-α (either approved or experimental, e.g., etanercept, infliximab, adalimumab);
3. Intra-articular, peri-articular, intramuscular or IV corticosteroids;
4. DMARDs other than MTX, e.g., hydroxychloroquine, sulfasalazine, leflunomide, gold, cyclosporin, D-penicillamine, azathioprine;
5. Hyaluronic acid injections;
6. Oral corticosteroids, NSAIDs, or COX-2 specific inhibitors unless at a stabilized dose for 4 weeks before enrollment and remained at that dose during the study. Stabilized oral corticosteroids must have been ≤ 10 mg prednisone or equivalent/day. Corticosteroids for dermatological use and nasal sprays were allowed;
7. For treatment of an RA flare or other painful conditions, paracetamol/acetaminophen (limited to ≤ 2 g per day prior to Amendment 3), codeine, oxycodone, hydrocodone, propoxyphene and tramadol were allowed (after Amendment 3) for no more than 3 consecutive days and on no more than 2 occasions. The use of these analgesics was not allowed within 24 hours prior to the arthritis assessments at any visit. The reason for use of these analgesics must have been recorded in the CRF. The use of other analgesics was not permitted. Continuous treatment with aspirin ≤ 325 mg/day stable for at least 28 days prior to the first dose of study medication for non-arthritic indication was permitted;
8. Supplements taken for reasons related to arthritis (such as glucosamine or chondroitin sulphate) were discouraged. However if these medications were taken they were to be maintained at a stable dose throughout the study, and were recorded as concomitant medications;
9. Vaccinations (killed, live, or attenuated). Vaccinations against influenza with inactivated virus were allowed (after Amendment 3).

Rescue Medication – 014

The use of rescue medication was not allowed in Study 014. Prior to Amendment 3, acetaminophen ≤ 2 g/day for ≤ 3 consecutive days for non-RA pain was permitted except within 24 hours of arthritis assessments. After Amendment 3, provision was made for treatment of RA flare or other conditions with acetaminophen, codeine, oxycodone, hydrocodone, propoxyphene or tramadol for ≤ 3 consecutive days and on no more than 2 occasions.

Study Schedule of Visits and Events - 014

The schedule of study visits and events are listed **Table 13.**

Table 13. Schedule of Study Visits – Study 014

Protocol Activities and Forms to be Completed	Screening (a)												
	Up to 35 Days Prior to Baseline Visit	Baseline	Week 1 (±2 d)	Week 2 (±3 d)	Week 4 (±5 d)	Week 8 (±5 d)	Week 12 (±5 d)	Week 16 (±5 d)	Week 20 (+/- 5 d)	Week 21 (+/- 3 d)	Week 22 (+/- 3 d)	Week 24 (±5 d) or Early Withdrawal	Week 4, 8, 12 Post Last Dose (b)(c)
Informed Consent	X												
Medical History	X												
Physical Exam	X											X	
Vital Signs(d)	X	X	X	X	X	X	X	X	X			X	X
Clinical Lab Tests(e)	X	X		X	X	X	X	X	X			X	X
Rheumatoid Factor	X												
Pregnancy Test(f)	X	X			X	X	X	X	X			X	X(f)
Chest X-ray(g)	X											X	
Electrocardiogram (ECG)	X											X	
PPD skin test	X												
Arthritis Assessments(h)	X	X	X	X	X	X	X	X	X			X	
Health Outcomes Measures													
SF-36		X			X		X					X	
EQ-5D		X			X		X					X	
Fatigue Assessment		X	X	X	X		X					X	
Work Productivity Survey		X			X	X	X	X	X			X	

Table 13. Continued.

Protocol Activities and Forms to be Completed	Screening (a)												
	Up to 35 Days Prior to Baseline Visit	Baseline	Week 1 (±2 d)	Week 2 (±3 d)	Week 4 (±5 d)	Week 8 (±5 d)	Week 12 (±5 d)	Week 16 (±5 d)	Week 20 (+/- 5 d)	Week 21 (+/- 3 d)	Week 22 (+/- 3 d)	Week 24 (±5 d) or Early Withdrawal	Week 4, 8, 12 Post Last Dose (b)(c)
Healthcare Resource Utilization (HCRU)					X		X					X	
Study Medication Administration		X			X	X	X	X	X				
IVRS(i)	X	X			X	X	X	X	X			X	
Concomitant Medication(j)	X	X	X	X	X	X	X	X	X			X	X
Adverse Events(k)		X	X	X	X	X	X	X	X			X	X
Plasma Samples for CDP870		X	X	X	X	X	X	X	X	X	X	X	X
Plasma Samples for Anti-CDP870 Antibody Testing		X	X	X	X	X	X	X	X	X	X	X	X
Plasma Samples for MTX		X					X					X	
Plasma Samples for Autoantibody Testing		X										X	

See Footnotes for Schedule of Events on following page.

Footnotes for Schedule of Events

(a) The following activities were undertaken at the Screening visit and were not captured on the case report form (CRF): informed consent, physical examination, vital signs, clinical laboratory tests, pregnancy test, urinalysis, and arthritis assessments.
(b) Follow-up visits 4, 8, and 12 weeks post last dose were not required if the patient entered the open-label safety study (015).
(c) Week 4 Follow-up Visit was not required if patient completed the Week 24 or Early Withdrawal Visit. The Week 8 follow-up visit could have been a telephone visit, only the urine pregnancy test was conducted.

Table 13. Continued.

Protocol Activities and Forms to be Completed	Screening (a)												
	Up to 35 Days Prior to Baseline Visit	Baseline	Week 1 (±2 d)	Week 2 (±3 d)	Week 4 (±5 d)	Week 8 (±5 d)	Week 12 (±5 d)	Week 16 (±5 d)	Week 20 (+/- 5 d)	Week 21 (+/- 3 d)	Week 22 (+/- 3 d)	Week 24 (±5 d) or Early Withdrawal	Week 4, 8, 12 Post Last Dose (b)(c)

Primary Efficacy Endpoint - 014

- ACR20 Response at Week 24

Secondary Efficacy Endpoints - 014

1. ACR50/70 (as for ACR20 but with reductions of 50% and 70%, respectively);
2. Tender/Painful Joint count;
3. Swollen Joint Count;
4. Patient's Assessment of Pain (VAS);
5. Patient's Global Assessment of Arthritis;
6. Physician's Global Assessment of Arthritis;
7. HAQ-DI;
8. CRP;
9. ESR;
10. Duration of morning stiffness;
11. Incidence of and time to withdrawal from the study due to lack of arthritis efficacy.

Exploratory Efficacy Endpoints - 014

1. EQ-5D

The EQ-5D comprises 5 health status measures and a visual analogue rating scale. The EQ-5D measures mobility, self-care, usual activities, pain discomfort, and anxiety/depression. Responses to each of the 5 health states were measured on a 3-point scale. This instrument was completed by the patient. The form was then checked by site staff for completeness.

2. Fatigue Assessments
3. Tender/Painful Joint count
4. Swollen Joint Count;
5. Patient's Assessment of Pain (VAS);
6. Patient's Global Assessment of Arthritis;
7. Physician's Global Assessment of Arthritis;
8. HAQ-DI;
9. Duration of Morning Stiffness
10. Acute Phase Reactants, CRP

Drug Concentration Measurements - 014

1. Plasma concentrations of CZP at Baseline, Weeks 1, 2, 4, 8, 12, 16, 20, 21, 22 and 24/ET and at 4 and 12 Weeks post final dose.
2. Determination of antibodies to CZP at Baseline, Weeks 1, 4, 8, 12, 16, 20, 21, 22, and 24/ET and at 12 Weeks post final dose.
3. Methotrexate and 7-hyroxy Methotrexate

Safety - 014

Safety was assessed by monitoring of AEs, clinical laboratory data (chemistry, hematology and urinalysis), vital signs, chest X-ray, 12-lead electrocardiogram (ECG) data and presence of auto-antibodies (anti-nuclear factor [anti nuclear antigen {ANA}], anti-double stranded (ds) DNA, anti-cardiolipin [immunoglobulin G (IgG) and immunoglobulin M (IgM)]) were assessed at screening or baseline and again at Week 24 or early termination (ET). All SAEs, whether or not they were related to the study medication, were to be reported by the Investigator immediately upon learning about the SAE.

Statistical Methods - 014

Analyzed Populations

A patient would be included in the modified Intent-to-Treat (mITT) cohort if he or she were randomized to treatment and had taken at least one dose of study medication. All efficacy analyses would be performed on the mITT cohort. Although statistical analyses specified in the protocol included controlling for site, due to the small number of patients within each site, sites within a country will be pooled and country used as the controlling factor in the statistical analyses.

Patient Withdrawal and Sensitivity Analyses

Patients withdrawing before Week 12, regardless of their final outcomes, would be considered as ACR20 non-responders at Week 24. A patient (who would drop out at or after Week 12 and would be ACR20 non-responder at the time of withdrawal) would be considered an ACR20 non responder at Week 24. The remaining PBO patients who would withdraw from the study at or

after Week 12 would be considered as ACR20 responders at Week 24 if they would be ACR- 20 responders at the time of withdrawal. The remaining patients assigned to treatment with CZP would be considered as ACR20 responders at Week 24 if the withdrawals would occur at or after Week 12 and if they would be ACR20 responders at the time of withdrawal and also at the last visit prior to the withdrawal. Remaining CZP patients who would drop out of the study at or after Week 12 would be considered as ACR20 non-responders at Week 24 if they do not satisfy the consecutive criteria described above. The CMH test, stratified by country, would be used for the sensitivity analysis.

Interim Analysis - 014

An interim analysis of Study 014 was performed by Pfizer for the purpose of planning future study design. The interim analysis was prospectively planned and mentioned in Study 014 protocol from the outset. After all patients had the opportunity to complete Week 12 of the study, the data were collected and analyzed by external consultants, i.e., a data safety monitoring board (DSMB). A letter summarizing the results of the DSMB review was provided to Pfizer. This letter provided qualitative feedback regarding between-group comparability and related issues, safety, efficacy, immunogenicity, and PK response. The sponsor states that the results from the interim analysis were not used to influence the conduct of later studies and procedures were followed to avoid compromising the blinding of other study personnel.

Protocol Deviations and Violations - 014

A total of 86 patients, 46 randomized to PBO + MTX and 40 to CZP 400 mg + MTX had 1 or more protocol deviations that were considered potentially relevant to the analysis of efficacy or safety based on blinded review of the data. A total of 65 efficacy deviations in 42 patients and 11 safety deviations in 10 patients were noted in the PBO + MTX group. In CZP 400 mg + MTX groups, 57 efficacy deviations in 34 patients and 14 safety deviations in 13 patients were noted. One patient, randomized to CZP 400 mg + MTX was withdrawn because of a protocol violation. Protocol deviations were excluded as part of the sensitivity analyses and did not affect the outcome of the statistical analyses.

Study CDP870 – 011 (Study 011)

Title - 011

Efficacy and Safety of CDP870 400 mg Subcutaneously versus Placebo in the Treatment of the Signs and Symptoms of Patients with Rheumatoid Arthritis Who Have Previously Failed at Least One DMARD (Study period from June 13, 2003 to July 12, 2004)

Primary Objective - 011

The primary objective was to compare the efficacy of CZP 400 mg q4w to placebo in treating the signs and symptoms of patients with RA who have previously failed at least one Disease Modifying Anti-Rheumatic Drug (DMARD).

Secondary Objectives - 011

The following were secondary objectives:

1. To evaluate the safety and tolerability of CZP 400 mg sc q4w;

2. To characterize the effect of CZP on health-outcomes measures;
3. To determine systemic exposures and the immunogenic profile of CZP.

Study Design and Conduct - 011
Study 011 was a multicenter, double-blind, randomized, placebo-controlled study which assessed the efficacy and safety of CZP 400 mg sc q4w as monotherapy. Between Screening (up to 35 days prior to the first dose of study drug) and Baseline, eligible patients were enrolled and randomized at a ratio of 1:1 to the CZP treatment group and the PBO group. All patients received either CZP 400 mg or PBO (SC) q4w for a total of 6 injections. The duration of treatment was 24 weeks with visits at Baseline, and Weeks 1, 2, 4, 8, 12, 16, 20, 21, 22 and 24. Patients who completed the study or who withdrew on or after the Week 12 visit were eligible to participate in the open-label safety study (Study 015), unless they were withdrawn from the current study due to non- compliance or a possible study drug related AE. If a patient did not participate in the open-label the follow-up visits occurred 4 and 12 weeks after the last dose of study drug.

Study Population and Sample Size - 011
It was anticipated that a minimum of 250 patients would be screened in order to randomize 200 patients (100 per treatment arm).

Inclusion Criteria – 011
Patients who met all of the following criteria were eligible for enrollment into the study:
1. 18 to 75 years of age, inclusive;
2. If female and of childbearing potential, she agreed to participate in this study by providing written informed consent, had been using adequate contraception since her last menses, was to use adequate contraception during the study and for 12 weeks after the study, was not lactating, and had a negative serum pregnancy test at screening, and negative urine test on the day of receiving the first dose of study drug;
3. Had a diagnosis of adult-onset RA of at least six months duration as defined by the 1987 ACR classification criteria;
4. Had active disease at Screening and Baseline as defined by:
    - ≥9 tender joints (68 joint count);
    - ≥9 swollen joints (66 joint count) and fulfilling 1 of the following 3 criteria:
    - ≥45 minutes duration of morning stiffness,
    - ≥28 mm/hour Erythrocyte Sedimentation Rate (ESR) [Westergren], or
    - CRP > 10 mg/L (> 1.0 mg/dL);
5. A history of failure to respond (i.e. either lack of efficacy or intolerance) to at least one DMARD;
6. Discontinued all DMARD therapy at least 28 days or five half-lives, whatever was longer, prior to first dose of study drug (after Amendment 4: exceptions, leflunomide wash out was to follow the drug elimination procedure listed in the Physicians' Desk Reference (PDR); hydrochloroquine was to be discontinued at least 28 days prior to first dose);
7. Provided written informed consent before undergoing any study procedures.

Exclusion Criteria - 011

Patients could not enter the study if any of the following criteria applied:

1. A diagnosis of any other inflammatory arthritis, e.g. psoriatic arthritis or AS;
2. A secondary, non-inflammatory type of arthritis (e.g. osteoarthritis or fibromyalgia) that in the Investigator's opinion was symptomatic enough to interfere with evaluation of the effect of CZP on the patient's primary diagnosis of RA;
3. A history of chronic infection, recent serious or life-threatening infection (within 6 months, including herpes zoster), or any current sign or symptom that might indicate an infection (e.g. fever, cough);
4. A history of tuberculosis or positive chest X-ray for tuberculosis or positive (defined as positive induration per local medical practice) purified protein derivative (PPD) skin test (Mantoux test). Patients with a positive PPD skin test who had received bacilli Calmette-Guérin (BCG) vaccination and had a negative chest X-ray for tuberculosis could be enrolled;
5. A history of an infected joint prosthesis at any time with prosthesis still *in situ*;
6. A positive hepatitis B surface antigen test and/or hepatitis C antibody test result during the pre-treatment period;
7. Receipt of any vaccination (live, attenuated, or killed) within 4 weeks prior to Baseline. Vaccinations against influenza with inactivated virus and vaccinations against pneumococcal diseases were allowed;
8. Active malignancy of any type or a history of malignancy, except basal cell carcinoma of the skin that had been excised prior to study start;
9. Current or recent history of severe, progressive, and/or uncontrolled renal, hepatic, hematological, GI, endocrine, pulmonary, cardiac, neurological, or cerebral disease;
10. Known human immunodeficiency virus (HIV) infection;
11. New York Heart Association (NYHA) class III-IV congestive heart failure requiring medical treatment;
12. A history of, or suspected, demyelinating disease of the central nervous system (e.g. multiple sclerosis or optic neuritis);
13. Uncontrolled diabetes mellitus type I or type II as defined as glycosylated hemoglobin (HbA1c) $\geq$ 8.5%;
14. Persistently abnormal aspartate aminotransferase (AST) or alanine aminotransferase (ALT) results, i.e. > 2.0 times the upper limit of normal;
15. Hemoglobin levels < 9 g/dl or hematocrit < 30%;
16. Total white blood cell (WBC) count of < 3.0 x 109/L (< 3000/mm3);
17. Platelet count < 100 x 109/L (< 100,000/mm3);
18. Serum creatinine above 1.5 times the upper limit of normal for the patient based on their age and sex;
19. Concurrent use of NSAIDs or COX-2 specific inhibitors unless the dose was stabilized for 4 weeks prior to enrollment into the study and would not change during the study;
20. Use of analgesics within 4 days prior to Baseline assessments (paracetamol/ acetaminophen within 24 hours). Continuous treatment with aspirin $\leq$ 325 mg/day for non-arthritic reasons, provided the dose of aspirin had been stable for at least 28 days prior to the first dose of CZP, was permitted;

21. Concurrent use of oral corticosteroids unless at a stabilized dose of ≤ 10 mg/day prednisone (or its equivalent) for 4 weeks prior to enrollment into the study and remaining at that dose during the study. Corticosteroids for dermatological use and as a nasal spray were permitted;
22. Intra-articular, periarticular, intramuscular, or IV corticosteroids in the 4 weeks preceding dosing;
23. Injection(s) of hyaluronic acid in the 4 weeks prior to the Baseline visit;
24. Receipt of any experimental therapy within 30 days prior to Screening;
25. Receipt of any biological therapies for RA within 6 months prior to study entry or any prior treatment with a TNF blocking agent including CZP;
26. A history of an adverse reaction to polyethylene glycol (PEG) or murine- derived product;
27. The patient was wheelchair-bound or bedridden; or any other condition which, in the Investigator's judgment, would make the patient unsuitable for inclusion in the study.

Removal of Patients from Study - 011
A patient could have been withdrawn from the trial treatment if, in the opinion of the Investigator, it was medically necessary, or if it was the wish of the patient. This section is consistent with that written for Study 014.

Treatment - 011
Each patient either received CZP 400 mg or PBO together with their permitted concomitant medications. The investigational drug supplies, provided by Pharmacia/Pfizer Corporation, consisted of the following:

- CZP for injection: 200 mg/vial, lyophilized powder in 5 mL glass vial;
- PBO for CZP: 70% weight-to-weight (w/w) sorbitol solution in 5 mL glass vial.

Dose Selection – 011
An earlier multi-center, double-blind, placebo-controlled, two-panel study (Study 004) assessed the safety and efficacy of doses of SC 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, and 800 mg of CZP versus PBO after 12 weeks (study drug administered at 0, 4, and 8 weeks) with open-label treatment of 400 mg q4w, thereafter. The results showed that doses of CZP ≥ 400 mg had clinical activity in treating the signs and symptoms of RA. At Week 12, ACR20 responder rates were 15%, 21%, 20%, 34% and 60% for PBO, CZP 50 mg, 100 mg, 200 mg, and 400 mg, respectively, in panel 1. In panel 2, ACR20 responder rates at Week 12 were 19%, 64%, and 79% for PBO, CZP 600 mg, and CZP 800 mg, respectively. In addition, data from the OL segment of the study demonstrated that administration on a 4-weekly basis for up to 2 years was well tolerated.

Prior and Concomitant Medications - 011
The following medications were prohibited for the duration of Study 011:
1. Any experimental therapy or biological therapy;
2. Any biological response modifier that blocked TNF-α (either approved or experimental, e.g. etanercept, infliximab, adalimumab);
3. Intra-articular, periarticular, intramuscular or IV corticosteroids;
4. DMARDs, e.g. hydroxychloroquine, methotrexate, leflunomide, gold, cyclosporin, D-penicillamine, azathioprine;

5. Hyaluronic acid injections;
6. Oral corticosteroids, NSAIDs, or COX-2 specific inhibitors unless at a stabilized dose for 4 weeks prior to enrollment into the study and remaining at that dose during the study. Stabilized oral corticosteroids must be ≤ 10 mg prednisone or equivalent/day. Corticosteroids for dermatological use and nasal spray were allowed;
7. For treatment of a RA flare or other painful conditions, paracetamol/acetaminophen, codeine, oxycodone, hydrocodone, propoxyphene and tramadol were allowed for no more than 3 consecutive days and on no more than 2 occasions. The use of these analgesics was not allowed within 24 hours prior to the arthritis assessments at any visit. The reason for use of these analgesics was recorded in the CRF. The use of other analgesics was not permitted. Continuous treatment with aspirin ≤ 325 mg/day stable for at least 28 days prior to the first dose of study drug for a non-arthritic indication was permitted;
8. Supplements taken for reasons related to arthritis (such as glucosamine or chondroitin sulphate) were to be discouraged. However, if these medications were taken, they were to be maintained at a stable dose throughout the study and were recorded as concomitant medications;
9. Vaccinations (killed, live or attenuated). Vaccinations against influenza with inactivated virus and against pneumococcal diseases were allowed.

Rescue Medication - 011

As explained by the sponsor, the use of rescue medication was not specifically captured in Study 011. Any medications taken for rescue purposes were captured as part of the concomitant medication data. Investigators were instructed to record the use of any concomitant medications, including over-the-counter medications, in the CRF. The use of such medication was reviewed during the blinded protocol deviation review and where applicable, was considered a protocol violation. Patients so identified were excluded from the sensitivity analyses for the appropriate variables and the Statistical Analysis Plan for a description of the sensitivity analyses).

Study Schedule of Visits and Events - 011

The study schedule of visits and events are listed in **Table 14.** Patients were required to visit the study site up to 12 visits, depending on whether they completed the study: Screening, Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 21, Week 22, and Week 24. Additionally, follow-up visits following Week 24 were required: Follow-up Week 4 (4 weeks after last dose), Follow-up Week 8 (for women participating in Austria), and Follow-up Week 12.

Table 14. Study Schedule of Visits – Study 011 (sponsor Table 9.5.1.1, pages 49 to 51 of 5470)

Protocol Activities and Forms to be Completed	Screening [(j)] Up to 35 Days Prior to Baseline Visit	Baseline	Days 1-6 [(k)]	Week 1 (±2 d)	Week 2 (±3 d)	Week 4 (±5 d)	Week 8 (±5 d)	Week 12 (±5 d)	Week 16 (±5 d)	Week 20 (±5 d)	Week 21 (±3 d)	Week 22 (±3 d)	Week 24 (±5 d) or Early Withdrawal	Week 4+8+12 Post Last Dose [(l)(m)]
Informed Consent	X													
Medical History	X													
Physical Exam	X												X	
Vital Signs[(c)]	X	X		X	X	X	X	X	X	X			X	X
Clinical Lab Tests[(b)]	X	X		X	X	X	X	X	X	X			X	X
Rheumatoid Factor		X												
Pregnancy Test[(e)]	X	X				X	X	X	X	X			X	X
Chest X-ray[(d)]	X												X	
12-Lead Electrocardiogram (ECG)	X												X	
PPD skin test	X													
Arthritis Assessments[(e)]	X	X		X	X	X	X	X	X	X			X	
Health Outcomes Measures														
SF-36		X				X		X					X	
Fatigue Assessment		X	X	X	X	X		X					X	
Work Productivity Survey		X				X	X	X	X	X			X	

Protocol Activities and Forms to be Completed	Screening [(j)] Up to 35 Days Prior to Baseline Visit	Baseline	Days 1-6 [(k)]	Week 1 (±2 d)	Week 2 (±3 d)	Week 4 (±5 d)	Week 8 (±5 d)	Week 12 (±5 d)	Week 16 (±5 d)	Week 20 (±5 d)	Week 21 (±3 d)	Week 22 (±3 d)	Week 24 (±5 d) or Early Withdrawal	Week 4+8+12 Post Last Dose [(l)(m)]
Healthcare Resource Utilization (HCRU)						X		X					X	
Functional Status Assessment		X	X	X									X	
Modified Brief Pain Inventory (pain intensity)		X	X	X										
Study Drug Administration		X				X	X	X	X	X				
IVRS[(f)]	X	X				X	X	X	X	X			X	X
Concomitant Medication[(g)]	X	X		X	X	X	X	X	X	X			X	X
AEs[(h)]		X		X	X	X	X	X	X	X			X	X
Plasma Samples for CDP870 and anti-CDP-870 analyses		X		X	X	X	X	X	X	X	X	X	X	X
Plasma Samples for Autoantibody Testing[(i)]		X											X	

(a) Vital Signs (sitting):
Screening: pulse, systolic/diastolic blood pressure, temperature and respiration rate;
Baseline: height, weight, pulse, systolic/diastolic blood pressure, temperature and respiration rate to be measured within 15 mins prior to dosing, with blood pressure and pulse repeated 30 mins after dosing with study drug;
Week 1, Week 2, 4 and 12 weeks post last dose: pulse, systolic/diastolic blood pressure, temperature and respiration rate;
Week 4 - Week 20: pulse, systolic/diastolic blood pressure, temperature and respiration rate to be measured within 15 mins prior to dosing, with blood pressure and pulse repeated 30 mins after dosing with study drug;
Week 24 (or early withdrawal visit): weight, pulse, systolic/diastolic blood pressure, temperature and respiration rate.

Table 14. Continued

Protocol Activities and Forms to be Completed	Screening [(j)] Up to 35 Days Prior to Baseline Visit	Baseline	Days 1-6 [(k)]	Week 1 (±2 d)	Week 2 (±3 d)	Week 4 (±5 d)	Week 8 (±5 d)	Week 12 (±5 d)	Week 16 (±5 d)	Week 20 (±5 d)	Week 21 (±3 d)	Week 22 (±3 d)	Week 24 (±5 d) or Early Withdrawal	Week 4+8+12 Post Last Dose [(l)(m)]

Primary Efficacy Endpoint - 011
ACR20 Responder Rate at Week 24

Secondary Efficacy Endpoints - 011
1. ACR50 and ACR70 Responder Rates;
2. Tender/Painful Joint Count;
3. Swollen Joint Count;
4. Patient's Assessment of Arthritis Pain (VAS);
5. Patient's Global Assessment of Arthritis;
6. Physician's Global Assessment of Arthritis;
7. Health Assessment Questionnaire Disability Index (HAQ-DI);
8. C-Reactive Protein (CRP);
9. Erythrocyte Sedimentation Rate (ESR);
10. Duration of Morning Stiffness;
11. Disease Activity Score (DAS);
12. Incidence of and Time to Withdrawal due to Lack of Arthritis Efficacy.
13. Fatigue Assessment
14. SF-36
15. Work Productivity Survey
16. Health Care Resource Utilization (HCRU)

Exploratory Efficacy Endpoints - 011
1. Functional Status Assessment;
2. Modified Brief Pain Inventory;

Pharmacokinetics (PK) - 011
See the study flow chart for PK and plasma sample time-points. There were no pharmacodynamics (PD) performed in Study 011.

Safety - 011
The safety measurements for the study included assessment of AEs, clinical laboratory tests, vital signs, physical examinations, electrocardiograms and chest X-rays, Purified Protein Derivative (PPD) skin test (at screening), and the presence of auto-antibodies; anti-nuclear factors (ANA), anti-double strain DNA, and anti-cardiolipin (both IgG and IgM).

Statistical Methods - 011
Demographics and Baseline Characteristics
Treatment groups were compared as described for Study 014.

Evaluation of Arthritis Efficacy
See discussion of general efficacy endpoints in Section 6.1.1 of this review. The frequency of ACR20 responders/non-responders at Week 24 was compared using Cochran-Mantel-Haenzel (CMH) test controlling for country. Sensitivity analyses of the primary efficacy variable were conducted to assess the robustness of the primary analysis results. An analysis of responders to ACR50 and ACR70 criteria was carried out in the same way as for ACR20.

Protocol Deviations and Violations – 011

A total of 79 (36%) patients had one or more deviations for efficacy, safety criteria or inclusion and or exclusion criteria. A total of 50 (23%) patients, 28 (26%) randomized to PBO and 22 (20%) to CZP 400 mg had 1 or more protocol deviations with respect to the validity of efficacy assessments. A total of 32 efficacy deviations in 28 patients and 2 safety deviations in 2 patients were noted in the PBO group. (See **Table 15**.)

In the CZP 400 mg group, 30 efficacy deviations in 22 patients and 2 safety deviations in 2 patients were noted. A total of 5 (2%) patients, 1 (0.9%) of whom had received PBO and 4 (4%) had received CZP 400 mg were withdrawn because of one of more protocol violations. Protocol deviations were excluded as part of the sensitivity analyses and did not affect the outcome of the statistical analyses.

Table 15. Number of Patients with Protocol Deviations by Treatment Group and Category, All Randomized Patients Sponsor Table 10:4, page 102 of 5470

Category of Deviation	Placebo (N = 109)	CDP870 400 mg (N = 111)
Patients with any deviations	45 (41.3%)	33 (29.7%)
Patients with 1 or more efficacy deviations	28 (25.7%)	22 (19.8%)
Number of efficacy deviations	32	30
Patients with 1 or more safety deviations	2 (1.8%)	2 (1.8%)
Number of safety deviations	2	2
Patients with 1 or more inclusion/exclusion deviations	19 (17.4%)	18 (16.2%)
Patients with inclusion deviations	17 (15.6%)	13 (11.7%)
Patients with exclusion deviations	2 (1.8%)	5 (4.5%)

Substudy within Study 051 (Substudy 051)
Prefilled Syringe Assessment with the Self-Injection Assessment Questionnaire© (SIAQ)

Title – Substudy 051

Phase 3 multi-center, open-label, follow-up study to Study 050, to assess the safety and efficacy of liquid CZP in combination with background MTX in the treatment of active rheumatoid arthritis.

Primary Objective - Substudy 051

The objective of Substudy 051 investigation was to report the RA patients' ability to self-inject CZP and the ease of handling and administration of the Prefilled Syringe (PFS) by employing the Self-Injection Assessment Questionnaire (SIAQ©).

Study Rationale, Design and Conduct - Substudy 051

Since no validated instrument is available to study the usability of a self-injection in RA patients, UCB developed the Self-Injection Assessment Questionnaire© (SIAQ©). In order to collect data

on the number of patients who are able to self-inject CZP and to document the ease of handling of the PFS, the SIAQ© was included in Substudy 051. Limitations in manual dexterity can be a barrier to self-injection for some RA patients. The applicant reports that in studies with other TNF blocker agents for RA patients opting to self-inject, 89% of those rated their impression of a self-injection instrument as "favorable" or "extremely favorable".

Amendment 2:
The protocol for Substudy 051 allowed patients in the United States of America, Poland and Czech Republic to self-inject CZP using the PFS at 3 consecutive visits. Data collected from patient completion of the SIAQ© at each self-injection visit was conducted as a sub-study within Study 051. A brief description follows:

- A patients' ability to self-inject and their ease of handling and administration with the PFS was based on patient responses to the SIAQ© in those patients who completed 3 consecutive self-injections.
- The concepts were assessed by summarizing the number and percentage of patients responding to each response option of items 5 to 7 (items of the "Your feelings about giving yourself an injection" domain) and items 11 to 15 (items of the "Features of the self-injection" domain) of the SIAQ©.

Study Population – Substudy 051

- 98 patients entered Substudy 051.

Outcome Instrument - SIAQ©

The SIAQ© is an instrument for use across different patient populations (RA and Crohn's Disease) to assess from the patient's perspective, their ability to self-inject a treatment and the ease of use of the PFS. The SIAQ© assesses the perceived advantages, potential limitations, and the willingness to continue self-injection. As noted in **Table 16,** two modules (23-items) of the SIAQ© were to be completed by patients:

1) The PRE-Self-Injection module (8 items) administered just before the first self-injection, and
2) The POST-Self-Injection module (23 items) administered after a self injection. Patients were advised to complete the POST Self-Injection module based on the combined experience from the two injections of CZP.

Table 16. SIAQ© Domains and Concepts Assessed

Domain	Concepts assessed
"Injections in general"	Feelings about injections in general
"Your feelings about giving yourself an injection"	Self-confidence in performing the injection and self-image
"Pain and skin reactions during or after the injection"	Burden of injection site reactions
"Features of the self-injection device"	Usability (ease of handling and administration) of the device
"Satisfaction with self-injection"	Convenience and satisfaction with self-injection
"Continuing self-injection"	Willingness to continue self-injection

Sponsor Table 3:1, page 8 0f 162

SIAQ© Variables

1. Patients ability to self-inject CZP
    - Completion of self-injections at 3 consecutive visits
    - Patient perception of ability to self-inject
2. Ease of handling and administration with the PFS

Statistical Methods

Descriptive statistics were employed to assess the SIAQ© POST-Self-Injection assessment. The analysis of items 11-15 were prospectively defined in the statistical analysis plan. Additionally, items 5-7 are also reported to document the patient's perspective of their ability to perform self-injections. See Section 6. Review of Efficacy, Section 6.5.4 Analysis of Primary Efficacy Endpoints for brief summary of Substudy 051.

6 Review of Efficacy

Summary of Overall Efficacy – Studies 027, 050, 014 and 011

In summary, the efficacy of CIMZIA® (CZP) in the treatment of the signs and symptoms of active RA was demonstrated by the results from the two pivotal Phase 3 randomized, placebo-controlled trials, Study 027 and 050, and from the two supportive Phase 3 randomized, placebo-controlled trials, Study 014 and 011. Both CZP dose regimens of 200 mg q2w + MTX and 400 mg q2w + MTX demonstrated comparative magnitudes of treatment effect as measured by the ACR20 response at Week 24, employing the lyophilized CZP formulation in Study 027 and employing the liquid formulation in Study 050. These outcomes support the proposed dosage and administration of CZP for adults as 400 mg at Week 0, 2 and 4 followed by 200 mg every other week.

In Study 027, the single CZP trial with co-primary efficacy endpoints, both CZP dose regimens demonstrated comparable treatment effect for the inhibition of progression of structural damage as measured by the change from Baseline in the modified Total sharp Score (mTSS) at week 52 and as a supportive key secondary efficacy endpoint at week 24 in Study 027. The CZP 200 mg and CZP 400 mg q2w + MTX groups showed 87% and 83% inhibition of progression of structural damage and at Week 52, demonstrated 85% and 92% inhibition of progression of structural damage in the same treatment groups, respectively.

This co-primary radiographic endpoint outcome in Study 027 at Week 24 was a key secondary endpoint in Study 050 and the outcome was comparable, 81% and 134% in the CZP 200 mg and 400 mg q2w + MTX groups for the magnitude of inhibition of progression of structural damage as measured by the change from Baseline in mTSS at Week 24 in Study 050. These outcomes support the proposed radiographic claim for CZP for inhibition of progression of structural damage in patients with active RA.

In Study 014, the CZP 400 mg q4w plus MTX compared to PBO + MTX showed efficacy as measured by the ACR20 response at Week 24 as 46% and 23%, respectively, in patients with active RA who had responded incompletely to MTX. In Study 011, the monotherapy dose

regimen of CZP 400 mg q4w compared to PBO alone demonstrated efficacy as measured by the ACR20 response at Week 24 as 46% for CZP compared to 9% for PBO in patients with active RA who had failed at least one DMARD. These outcomes support the proposed alternative dosage and administration of CZP 400 mg q4w as maintenance therapy for active RA.
The results of the primary efficacy endpoint, the ACR20 response in Study 027, 050, 014 and 011, and the co-primary efficacy endpoint, inhibition of progression of structural damage as measured by the change from Baseline in mTSS in Study 027 and in Study 050 as a key secondary endpoint, were all supported by the results of a variety of sensitivity analyses.

Support for the additional proposed claim of major clinical response was shown in Study 027 by the two key secondary endpoints, major clinical response, defined as ACR70 response at any two time-points 24 weeks apart during the study and at all assessments in between, and sustained response, defined as ACR20 responders at both week 24 and 52. In addition, support for the proposed claim of CZP ability to improve physical function were provided by the results of Study 027, 050, 014 and 011 as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) and supported by the Short-Form 36 Questionnaire (SF-36), Physical Component Summary (PCS).

6.1 Indication – Study 027

The CZP RA clinical development program was designed to support the following proposed indications in adults with active RA, unresponsive to MTX and or other DMARDs:

- Reducing the signs and symptoms,
- Major clinical response,
- Inhibiting the progression of structural damage,
- Improving physical function, (b) (4)

6.1.1 Methods – Study 027

The efficacy data contained in Section 6.1 of this review were generated from Study 027, a 52-week, randomized, PBO-controlled trial and were reviewed to assess the sponsor's efficacy submission. The analyses of the co-primary efficacy endpoints, the ACR response at Week 24 and inhibition of progression of structural damage as measured by the change from Baseline in the modified Total sharp Score (mTSS) at week 52, as well as the analyses of the secondary and exploratory endpoints were conducted for Study 027. All of the primary and secondary efficacy analyses were confirmed by the FDA's statistical reviewer, Katherine Meaker, PhD. The co-primary efficacy endpoints are discussed below in the General Discussion of Endpoints section. See Section 5.3 Discussion of Individual Studies.

General Discussion of Endpoints – Study 027
RA is one of the most common inflammatory arthritides. Patients with RA experience chronic articular pain, disability and have a higher mortality rate than patients in the general population. RA mainly affects the hands and feet, but may also affect larger weight-bearing and appendicular

joints. The goal for treatment of adult RA is to control the chronic inflammation of joints and prevent bony destruction and subsequently, improve a patient's activities and quality of life.

RA Guidance for Industry:
The FDA Guidance for Industry: Clinical Development Programs for Drugs, Devices, and Biologic Products Intended for the Treatment of Rheumatoid Arthritis (RA) is a reference for sponsors to consider during the clinical development of products proposed to treat RA. The guidance describes claims for the treatment of RA which include reduction in the signs and symptoms of RA, major clinical response defined as ACR70 response (e.g., a continuous 6-month period of success by the ACR-70), complete clinical response meeting ACR criteria for remission but on anti-rheumatic drugs remission (clinical improvement with greater magnitude than a major clinical response), remission, improvement in physical function, and slowing or inhibiting the progression of structural damage as demonstrated by using radiographic scoring methods that take into account both joint space narrowing and erosions, such as the Sharp Scoring system or its variants.

Improvement in Signs and Symptoms:
The claim for the treatment of RA includes the reduction in the signs and symptoms of RA, which is the demonstration of symptomatic benefit that include improvement in the signs of disease activity as well as symptoms. The 1987 American College of Rheumatology (ACR) definition of improvement (ACR20) is a validated and widely accepted composite endpoint that has become a standard primary outcome measure in RA clinical trials intended to demonstrate the benefit of reduction in signs and symptoms.[1] The definition of an ACR20 response requires ≥ 20% improvement in tender joint count (68 joints), ≥ 20% improvement in swollen joint count (66 joints) and ≥ 20% improvement in 3 of the following 5 core variables: 1) Patient pain assessment (VAS 100mm); 2) Patient global assessment of disease activity (VAS 100mm); 3) Physician global assessment of disease activity (VAS 100mm); 4) Patient self-assessed disability using the HAQ; and 5) Acute-phase reactant (ESR or CRP). The four Phase 3 CZP RA clinical trials employed the ACR20 as the primary efficacy endpoint.

Inhibition of the Progression of Structural Damage:
The sponsor conducted two clinical trials employing radiographic assessment of CZP in adult patients with RA. Study 027 included a co-primary efficacy endpoint for the inhibition of the progression of structural damage by assessing the degree of change in radiographic damage in patients' hands and feet using a modified total Sharp Score (mTSS) from Baseline to Week 52. Study 050 included a secondary endpoint, for the same radiographic assessment using the mTSS, from Baseline to Week 24. The mTSS is a validated radiographic scoring system based on blinded evaluation of bilateral x-rays of the hands and feet involving 21 hand/wrist joints and 6 bilateral foot joints. The Agency has approved products for radiographic inhibition based on the mTSS in adult patients with RA.

Improvement in Physical Function and Disability:
To assess improvement in physical function, the sponsor used the Health Assessment Questionnaire-Disability Index (HAQ-DI). The HAQ-DI is an instrument that has been validated for use in clinical trials in RA. It assesses the degree of difficult in carrying out various activities

of daily living. They also used the SF-36 physical component summary (PCS). The SF-36 PCS is a health status instrument that measures the impact of physical improvement on a variety of life activities.

Secondary Endpoints:
The sponsor also includes two additional secondary endpoints of Tiredness, assessed by the Fatigue Assessment Scale (FAS) and the SF-36 Vitality domains, and of Productivity, assessed by the Work Productivity Survey (WPS), in Studies 027, 050, and 011. (b) (4)

Additional secondary endpoints also included the assessment of the proportion of patients achieving an ACR20/50/70 based on a ≥ 20/50/70% improvement in the number of tender joints, swollen joints, and in 3 of the 5 core set measures (Patient's and Physician's Global Assessments of Disease Activity - VAS, Patient's Assessment of Arthritis Pain - VAS, CRP, and physical function based on the HAQ-DI) in Studies 027 and 050. In Studies 011 and 014, the secondary endpoint was for the assessment of the ACR50 and ACR70 responder rates at all visits.

The DAS28 score was included as another secondary endpoint. The DAS20 measures the level of disease activity in contrast to the proportion of patients achieving a level of improvement. The DAS28 is a continuous measure defined by 4 components: 28 tender joint count, 28 swollen joint count, ESR and the patient assessment of disease activity measured on a VAS 100mm scale. The scores for disease activity defined by the DAS28 are as follows: high is > 5.1; low is ≤ 3.2; clinically significant improvement is a change of ≥ 1.2; and remission is defined as < 2.6. Though the DAS28 includes a definition of remission, this is not comparable to the Agency's RA Guidance definition of remission because patients could continue to have swollen and tender joints and achieve the DAS28 criteria for remission. In addition to the clinical differences, the DAS28 definition of remission does not include radiographic findings of progression.

References
1. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31:315-324.
2. Fries JF, Spitz P, Kraines RG, Hokman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980; 23(2):137-45.

6.1.2 Demographics - Study 027 (and the three other Phase 3 Studies)

In Studies 027, 050, 011 and 014, the patient populations are generally well balanced among treatment groups and representative of adult RA patients with active disease. See **Table 17.** There was a somewhat longer disease duration in Study 011 (9.5 years) and 014 (9.6 years) compared to Study 027 (6 years) and to Study 050 (6.2 years), and a higher proportion of rheumatoid factor (RF) positive patients in Study 011 (100%) compared to 78%, 82% and 77% in Studies 014, 027 and 050, respectively. There were relatively fewer females in Study 014 (69%) contrasted with a larger proportion of females, 84%, 83%, and 82% in Studies 011, 027

and 050, respectively. Overall, the study populations were comparable at Baseline with respect to the variables of age, gender, race, height, weight, and body mass index (BMI).

The patient population in Study 027 was balanced across the three treatment groups, PBO + MTX, CZP 200 mg q2w + MTX and 400 mg q2w + MTX as demonstrated in **Table 18.**

Table 17. Summary: Demographic and Disease Characteristics, Phase 3 CZP RA Trials

Study	CDP870-011 N=220	CDP870-014 N=247	CDP870-027 N=982	CDP870-050 N=619
Age (years) Mean (SD)	53.8 (12.2)	54.3 (12.05)	52.0 (11.6)	51.9 (11.5)
Female (%)	83.6%	69.2%	83.2%	81.6%
Disease Duration (years) Mean (SD)	9.5 (NC)	9.6 (NC)	6.1 (4.3)	6.2 (4.2)
RF-positive [≥ 14 IU/mL] (%)	100%	78%	81.8%	76.9%
MTX dose (mg/week) Mean	N/A	16.8	13.6	12.5
Number of Previous DMARDS (Mean)	2.0	1.3	1.3	1.2
Tender Joint Count Mean (SD)	29.0 (13.13)	30.0 (12.28)	30.7 (12.9)	30.2 (14.0)
Swollen Joint Count Mean (SD)	20.5 (9.67)	22.5 (9.48)	21.5 (9.8)	21.0 (9.8)
HAQ-DI mean (SD)	1.5 (0.64)	1.4 (0.63)	1.7 (0.60)	1.6 (0.59)
CRP (mg/L) Geometric Mean (CV)	11.5 (ND)	12.4 (NC)	14.7 (144.2)	13.6 (180.9)
DAS28(ESR) Mean (SD)	6.3 (1.00)	6.2 (0.99)	6.9 (0.8)	6.8 (0.83)

Notes: CV = coefficient of variation; DAS = disease activity score; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; IU = international units; L = liter; mg = milligrams; mL = milliliters; RF= rheumatoid factor; SD = standard deviation; y = years; NC= not calculated; N/A=not applicable
(a) All randomized subjects; the actual numbers vary slightly across parameters
Source CSRs CDP870-011, CDP870-014, CDP870-027, and CDP870-050
Sponsor Table 2.5:2, page 17 of 52

Table 18. Demographic Characteristics – Study 027

Demographic Characteristics (ITT Population) Study CZP - 027				
Characteristics	PBO + MTX N = 199	CZP 200 mg q2w+MTX N = 393	CZP 400 mg q2w+MTX N = 390	Overall N = 982
Age (yrs) Mean (SD)	52 (11.2)	51 (11.6)	52 (12)	52 (12)
Median	52	52	53	52
Min., Max.	18, 78	19, 81	21, 83	18, 83
Age (yrs) ≤ 35	15 (8%)	37 (9%)	34 (9%)	86 (9%)
≥ 35 - < 45	22 (11%)	64 (16%)	57 (15%)	143 (15%)
≥ 45 - < 55	77 (39%)	127 (32%)	127 (33%)	331 (34%)
≥ 55 - < 65	59 (30%)	113 (29%)	113 (29%)	285 (29%)
≥ 65 - < 75	23 (12%)	47 (12%)	50 (13%)	120 (12%)
≥ 75	3 (2%)	5 (1%)	9 (2%)	17 (2%)
Gender Male	32 (16%)	69 (18%)	64 (16%)	165 (17%)
Female	167 (84%)	324 (82%)	326 (84%)	817 (83%)
Race Caucasian	179 (90%)	363 (92%)	349 (90%)	891 (91%)
African-American	2 (1%)	4 (1%)	2 (1%)	8 (1%)
Hispanic/Latin America	16 (8%)	20 (5%)	34 (9%)	70 (7%)
Other	2 (1%)	6 (2%)	5 (1%)	13 (1%)
Weight (kg) (n)	198	392	387	977
mean (SD)	74 (17)	74 (17)	73 (16)	73 (16)
min., max.	44, 142	43, 160	40, 141	40, 160
BMI (n) Mean (SD)	198	392	387	977
Mean (SD)	28 (6)	27 (6)	27 (6)	27 (6)
Min., Max.	16, 50	16, 50	15, 54	15, 54
BMI Class < 18.5 kg/m^2	7 (4%)	9 (2%)	9 (2%)	25 (3%)
18.5 kg/m^2 - < 25 kg/m^2	70 (35)	145 (37%)	143 (37%)	358 (37%)
25 kg/m^2 - < 30 kg/m^2	66 (33%)	135 (34%)	131 (34%)	332 (34%)
≥ 30 kg/m^2	55 (28%)	103 (26%)	104 (27%)	262 (27%)
Protocol Version				
Original	170 (85%)	353 (90%)	345 (89%)	868 (88%)
Amended	29 (15%)	40 (10%)	45 (12%)	114 (12%)

N = number of patients in treatment group; n = number of patients with data; MTX =methotrexate; BMI = Body mass index = body weight (kg) / (height (m2); q2w = every 2 weeks; SD = standard deviation; Revised from sponsor Table 11.2, page 87 of 8823.

6.1.3 Patient Disposition – Study 027

In Study 027, a total of 992 patients (across 147 centers in 22 countries) were randomized in a 1:2:2 ratio and 10 patients were excluded from the efficacy analysis. The Lithuania sites, No. 93 and 104, assigned to the clinical investigator, Dr. Paksys, were excluded (10 patients) because fraud and misconduct were documented at these sites and reported to Division of Scientific Investigations (DSI). Section 3.0 Ethics and Good Clinical Practices includes explanation for the issues of fraud and misconduct reported in the CZP RA program. The remaining 982 patients (199 patients in the PBO + MTX group, 393 patients in the CZP 200 mg q2w + MTX group, and 390 patients in the CZP 400 mg q2w + MTX group), were included in the ITT population for the analysis of efficacy. The final patient disposition is shown in **Figure 4** and **Table 19.**

The ITT population included a total of 572 (58%) patients and 597 (61%) who completed Study 027 through Week 52 and 24, respectively. Overall, 90% of patients in Study 027 had data

available (93%, 90% and 89% of patients in the PBO + MTX, CZP 200 mg and CZP 400 mg q2w + MTX treatment groups) to calculate the primary efficacy endpoint analysis for ACR20 percent of responders.

As demonstrated in **Table 19**, two-hundred and seventy-six (28%) of patients discontinued at Week 16 due to lack of efficacy and, overall, 410 (42%) of patients discontinued from Study 027. The most common reason for withdrawal was lack of efficacy, particularly at Week 16, due to the pre-specified protocol-mandated exit of ACR20 non-responders at Week 12 (confirmed at Week 14, pre-specified). As expected, the PBO + MTX group had the highest percentage of patients (71%) withdrawing due to lack of efficacy compared to 25% and 19% of patients in the CZP 200 mg q2w + MTX and CZP 400 mg q2w + MTX treatment groups, respectively, vs 2% of PBO controls. The next most common reason for withdrawal was adverse events, 4% and 6% of patients in CZP 200 mg q2w + MTX and CZP 400 mg q2w + MTX groups, respectively. Patients from Study 027 who left the study at Week 16 or completed at Week 24 were eligible to enter the open-label (OL) extension Study 028, and continue treatment with CZP.

Figure 4. Patient Disposition - Study 027
(Sponsor Figure 10:1, page 83 of 8823)

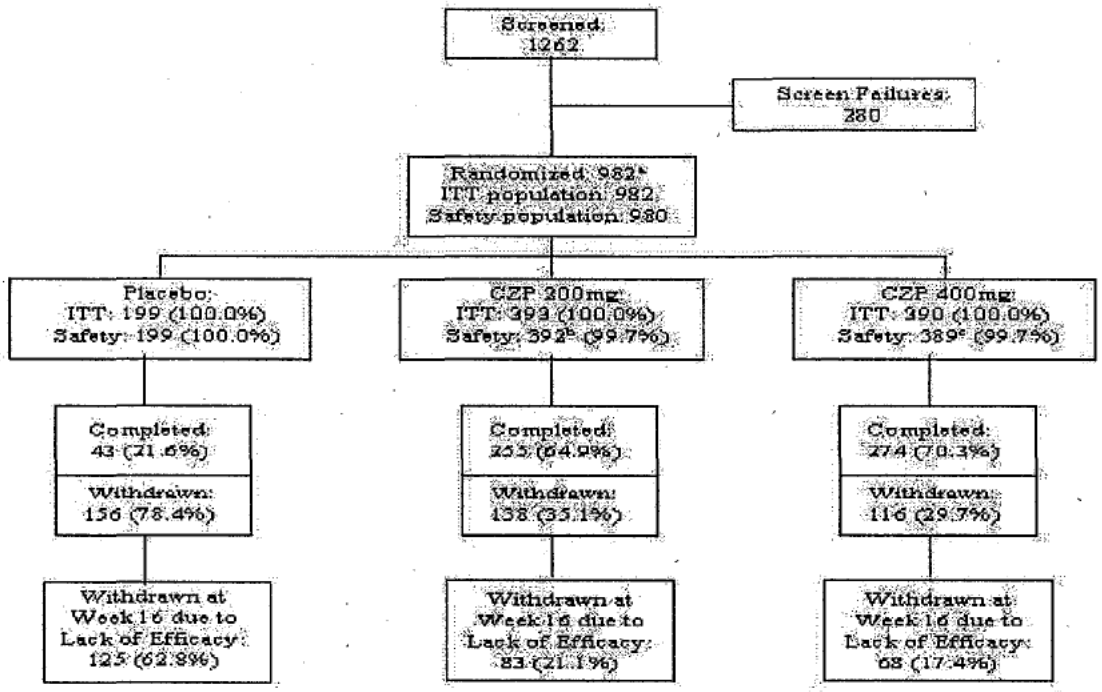


Table 19. Patient Disposition: Withdrawals (ITT) – Study 027

Patient Disposition - Study 027 (ITT Population)				
	PBO + MTX	CZP 200 mg q2w+MTX	CZP 400 q2w+MTX	Overall
All patients				1262 (100%)
Screening failures				280 (22%)
Randomized (ITT)	N = 199	N = 393	N = 390	N = 982 (100%)
Safety population	199 (100%)	392 (99.7%)	389 (99.7%)	980 (99.8%) [a]
PP (signs, symptoms)	192 (96%)	370 (94%)	378 (97%)	940 (96%)
PP (structural damage)	191 (96%)	371 (94%)	377 (97%)	939 (96%)
Withdrawn at Week 16	125 (63%)	83 (21%)	68 (17%)	276 (28%)
Completed at Week 16	173 (87%)	355 (90%)	357 (92%)	885 (90%)
Completed at Week 24	45 (23%)	264 (67%)	288 (74%)	597 (61%)
Completed at Week 52	43 (22%)	255 (65%)	274 (70%)	572 (58%)
Total Discontinuations	156 [c] (78%)	138 [c] (35%)	116 [c] (30%)	410 [c] (42%)
Lack of efficacy	141 (71%)	98 (25%)	74 (19%)	313 (32%)
Discontinued due to AEs	3 (2%)	17 (4%)	22 (6%)	42 (4%)
Protocol violations	0	4 (1%)	3 (0.8%)	7 (0.7%)
Patient decision, consent w/dr.	10 (5%)	15 (4%)	11 (3%)	36 (4%)
Lost to follow-up / Unknown	1 (0.5%)	1 (0.3%)	1 (0.3%)	3 (0.3%)
Other [b]	3 (2%)	5 (1%)	6 (2%)	14 (1.4%)
Pts. with non-missing data for the primary efficacy endpoint [d]	93%	90%	89%	90%

(a.) Two patients were randomized but did not receive study drug: Pt.# 118/004 randomized to 200 q2w+MTX withdrew her consent; Pt. #135/005 randomized to 400 q2w+MTX was discontinued due to abnormal ESR/CRP not meeting entry criteria.
(b.) One death (Pt. # 052/002) is reported in the PBO-control treatment group and one death (Pt. # 068/014) is reported in the 400 mg q2w + MTX treatment group. See safety review section for total number of deaths in Study CDP870-027.
(c.) Total discontinuations differ from table #: PBO-Control, 158 vs 156; 200 q2w+MTX, 140 vs 138 ; 400 q2w+MTX, 117 versus 116; Overall 410 vs 415. Abbreviations: PP = per protocol; AEs = adverse events; w/dr.=withdrawn.
(d.) Patients with adeqaute data who completed or dropped out due to lack of efficacy. Therefore, data is adeqaute to calculate the primary efficacy analysis for ACR20 responders at Week 52.
Revised from sponsor Table 14.1.1:2,page 261 of 8823.

Patients Randomized by Region and Country – Study 027

Study 027 was conducted in 147 clinical centers in 22 countries as follows: Argentina (12 centers), Chile (4), Mexico (3), Estonia (3), Finland (3), Latvia (3), Lithuania (6), Russia (10), Ukraine (10), Bulgaria (6), Croatia (1), Czech Republic (8), Hungary (7), Serbia (5), Slovakia (4), Australia (7), Belgium (4), Canada (13), France (2), Israel (7), New Zealand (5), and the United States (24). See **Table 20.** Due to questionable data and a serious breach of GCP at one site (Site No. 93) in Lithuania, the data from that site was excluded from the efficacy and safety analyses performed.

The highest percent of enrolled patients were in the Russian, Baltic States and Scandinavian Region (31%) and in the Eastern Europe Region (35%). The United States enrollment represents 7% of the Rest of the World Region (18%) and the Central and South American Region represents (16%) of all patients enrolled in Study 027.

Table 20. Patients Randomized by Geographical Region and Country – Study 027

Proportion of Patients Randomized by Region and Country - Study 027 (ITT Pop.)				
Region / Country	PBO + MTX N = 199	CZP 200 mg sc q2w + MTX N = 393	CZp 400 mg sc q2w + MTX N = 390	Overall N = 982
Central and South America	30 (15%)	60 (15%)	63 (16%)	153 (16%)
Argentina	27 (14%)	53 (14%)	53 (14%)	133 (14%)
Chile	5(1%)	6 (2%)	6 (2%)	13 (1%)
Mexico	1 (1%)	2 (1%)	4 (1%)	7 (1%)
Russia, Baltic States and Scandinavia	62 (31%)	123 (31%)	122 (31%)	301 (31%)
Estonia	4 (2%)	7 (2%)	7 (2%)	18 (2%)
Finland	1 (1%)	4 (1%)	3 (1%)	8 (1%)
Latvia	7 (4%)	11 (3%)	11 (3%)	29 (3%)
Lithuania	10 (5%)	19 (5%)	18 (5%)	47 (5%)
Russia	22 (11%)	48 (12%)	46 (12%)	116 (12%)
Ukraine	18 (9%)	34 (9%)	37 (10%)	89 (10%)
Eastern Europe	71 (36%)	141 (36%)	136 (35%)	348 (35%)
Bulgaria	8 (4%)	13 (3%)	14 (4%)	35 (4%)
Croatia	1 (1%)	2 (1%)	2 (1%)	5 (1%)
Czech Republic	27 (14%)	55 (14%)	50 (13%)	132 (13%)
Hungary	14 (7%)	30 (8%)	30 (8%)	74 (8%)
Serbia	11 (6%)	23 (6%)	20 (5%)	54 (6%)
Slovakia	10 (5%)	18 (5%)	20 (5%)	48 (5%)
Rest of the World	36 (18%)	69 (18%)	69 (18%)	174 (18%)
Australia	3 (2%)	7 (2%)	8 (2%)	18 (2%)
Belgium	1 (1%)	3 (1%)	4 (1%)	8 (1%)
Canada	6 (3%)	10 (3%)	10 (3%)	26 (3%)
France	1 (1%)	1 0%)	2 (1%)	4 (0%)
Israel	5 (3%)	10 (3%)	13 (3%)	28 (3%)
New Zealand	5 (3%)	10 (3%)	6 (2%)	21 (2%)
United States	15(8%)	28 (7%)	26 (7%)	69 (7%)
Revised from sponsor Table 11:3, page 88 of 8823.				

Disease Characteristics – Study 027

Overall, the reported history of adult RA and the disease characteristics, including disease duration, articular features, Baseline medication, previous steroid use, concomitant RA medication and previous TNF-inhibitor use were similar across the 3 treatment groups. The concomitant medications were typical of medications employed in the treatment of RA. See **Table 21.**

Table 21. Disease History and Baseline Characteristics – Study 027

Rheumatoid Arthritis History and Baseline Charteristics - Study 027				
	PBO + MTX N = 199	CZP 200 sc q2w+MTX N = 393	CZP 400 sc q2w+MTX N = 390	Overall N = 982
History Disease Duration (yrs.)[a]				
n	199	393	390	982
Mean (SD)	6 (4)	6 (4)	6 (4)	6 (4)
Disease Duration Class[a]				
≤ 3 years	57 (29%)	120 (31%)	126 (32%)	303 (31%)
> 3 years	142 (71%)	273 (70%)	264 (68%)	679 (69%)
Concomitant Methotrexate Dose (mg/week)				
n	198	392	389	979
Mean (SD)	13 (4)	14 (4)	14 (4)	16 (4)
Extra Articular Features (Any History)				
Nodules	55 (28%)	93 (24%)	80 (21%)	228 (23%)
Vasculitis	11 (6%)	6 (2%)	7 (2%)	24 (2%)
Neuropathy	10 (5%)	14 (4%)	11 (3%)	35 (4%)
Other location/site	21 (11%)	54 (14%)	54 (14%)	129 (13%)
Extra Articular Features (At Screening)				
Nodules	46 (23%)	74 (19%)	66 (17%)	186 (19%)
Vasculitis	4 (2%)	3 (1%)	7 (2%)	14 (1%)
Neuropathy	7 (4%)	10 (3%)	9 (2%)	26 (3%)
Other location/site	18 9%)	41 (11%)	44 (11%)	103 (11%)
Number of Previous DMARDS				
n	199	393	390	982
Mean (SD)	1.4 (1)	1.3 (1)	1.3 (1)	1.3 (1)
# of Previous DMARDS Class				
0	70 (35%)	128 (33%)	120 (31%)	318 (32%)
1	49 (25%)	135 (34%)	130 (33%)	314 (32%)
2	36 (1%)	61 (16%)	78 (20%)	175 (18%)
3	28 (14%)	40 (10%)	40 (10%)	108 (11%)
> 3	16 (8%)	29 (7%)	22 (6%)	67 (7%)
Baseline Steroid Use				
Yes	115 (58%)	238 (61%)	236 (61%)	589 (60%)
No	84 (42%)	155 (39%)	154 (40%)	393 (40%)
Previous Anti-TNF Use[b]				
Yes	7 (4%)	11 (3%)	16 (4%)	34 (4%)
No	192 (97%)	382 (97%)	374 (96%)	948 (97%)

(a.) Duration (years) at Screening visit.
(b.) Anti-TNF and other biological treatment is considered.
Revised from sponsor Table 11.4, page 89 of 8823.

Baseline Rheumatoid Arthritis Disease Characteristics – Study 027

The Baseline characteristics demonstrated that the population in Study 027 suffered from active RA with similar severity of tender/painful joint counts and swollen joint counts, as well as the patient's and the physician's global assessment of arthritis. The Baseline radiographic status was similar across the three treatment groups. See **Table 22.**

Table 22. Rheumatoid Arthritis Baseline Characteristics – Study 027

Rheumatoid Arthritis Baseline Charteristics - Study 027				
	PBO + MTX N = 199	CZP 200 mg q2w + MTX N = 393	CZP 400 mg q2w + MTX N = 390	Overall N = 982
Tender/painful jt. ct [a.] Median (min,max)	28 (9, 68)	29 (9, 68)	28 (6, 68)	28 (6, 68)
Swollen joint count [b.] Median (min,max)	20 (5, 66)	20 (6, 60)	18 (8, 56)	19 (5, 66)
Pt's Global Assess.. Arthritis Median (min,max) (0-100mm VAS)	67 (5, 99)	64 (1, 100)	67 (3, 99)	66 (1, 100)
Physician's Global Assessm. Median (min,max) of Arthritis (0-100mmmVAS)	66 (16, 100)	65 (21, 100)	64 (17, 100)	65 (16, 100)
Patient's Assess. Of Arth. Pain, Median (min,max) Arthritis Pain (0-100mmVAS)	65 (5, 100)	65 (3, 100)	65 (10, 100)	65 (3, 100)
HAQ Disability Index [c.] Median (min,max)	1.8 (0.1, 3)	1.8 (0, 3)	1.8 (0, 3)	1.8 (0,3)
FAS, Median (min,max)	7 (0, 10)	7 (0, 10)	7 (0, 10)	N/A (0, 10)
Duration of Morning Stiffness (hrs), Median (min,max)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)
DAS28 (ESR) [d.] Median (min, max)	7 (5, 8)	7 (4, 9)	7 (5, 9)	7 (4, 9)
DAS 28 (ESR) Class, < 3.2	0	0	0	0
3.2 - 5.1	3 (2%)	8 (2%)	4 (1%)	15 (2%)
> 5.1	196 (99%)	383 (98%)	385 (99%)	964 (99%)
CRP (mg/L), Geometric mean (CV)	16 (156)	15 (144)	14 (138)	15 (144)
CRP Class, Baseline CRP ≤ 15 mg/mL	98 (49%)	195 (47%)	209 (54%)	502 (51%)
Baseline CRP > 15 mg/L	101 (51%)	198 (50%)	181 (46%)	480 (49%)
ESR (mm/hr) Geometric Mean (CV)	48 (47%)	45 (52)	44 (50)	45 (50)
ESR Class, Baseline ESR < 30 mm/hr.	19 (10%)	44 (11%)	39 (10%)	102 (10%)
Baseline ESR ≥ 30 mm/hr.	180 (91%)	348 (89%)	351 (90%)	879 (87%)
Rheumatoid Factor (IU/mL), Median (min,max)	166 (230)	190 (273)	201 (587)	190 (421)
Rheumatoid Factor Class, Negative (, 14 IU/mL)	34 (17%)	80 (20%)	64 (16%)	178 (18%)
Positive (≥ 14 IU/mL)	164 (83%)	312 (80%)	326 (84%)	802 (82%)
mTSS, Median (Q1, Q3)	21 [8, 53]	20 [6,49]	19 [7, 52]	N.A.
Joint Erosion, Median [Q1, Q3]	7 [1, 19]	6 [0.5, 18]	5 [1, 16]	N. A.
Joint Space Narrowing Score, Median [Q1, Q3]	16 [5, 36]	13 [4, 35]	14 [4, 36]	N.A.
Revised from sponsor Table 14.1.4:5, page 321 - 326 of 8823 and Table 11.5, page 92 of 8823.				

(a.)Tender joint-count range from 0-68; (b.) Swollen joint count range from 0-66;
(c.) HAQ Disability Index (HAQ-DI) ranges from 0-448. (d.) DAS28 (ESR) = 0.56 x sqrt (number of tender/painful joints) + 28 x sqrt (number of swollen joints) + 70 x ln (ESR) + 0.014 x (patient's global assessment of arthritis VAS in mm), sqrt: square root, ln: heperian logarithm.
Abbreviations: VAS=Visual Analogue Scale; CRP= C-Reactive Protein; ESR = Erythrocyte Sedimentation Rate; CV= [Coefficient of Variation] (%) = sqrt [exp (sd log 2) – 1 * 100 where sd log represents the standard deviation of the log-transformed parameter.
Revised from sponsor Table 14.4:5, page 321-326 of 8823 and Table 11:5, page 92 of 8823.

Baseline PPD Tests – Study 027

A total of 61% of patients had no reaction to PPD skin tests at Screening (ITT population). Most patients who a reactive test had PPD indurations of 1 to 5 mm in diameter while the remainder of patients had indurations ≥ 6 mm in diameter, approximately 17%, overall. At the time of Study 027 (February 2005 to September 2006), patients with a history of vaccination with BCG were assumed to have positive PPD due to BCG vaccination.

Ongoing Phase 3 CZP RA studies were amended (August 2007) to include current guidelines, which require that a positive PPD would be assumed to reflect latent tuberculosis infection, regardless of whether or not the patient had previously received BCG. In this case, patients

would be treated for tuberculosis, based on the judgment of the treating physician, rather than assumed that the reason for a positive PPD is exposure to a past BCG vaccination.

Baseline Vital Signs – Study 027
The Baseline vital signs in Study 027 were similar across the treatment groups (mean temperature 36.45 degrees Centigrade, mean pulse rate 75 beats per minute (bpm), mean systolic blood pressure 127 mmHg, mean diastolic blood pressure 78 mmHg, and mean respiratory rate was 17 breaths per minute).

Concurrent Medications and Disease Modifying Anti-inflammatory Drugs – Study 027
The total number of patients taking at least 1 concurrent RA medication at Baseline was similar across the treatment groups: 198 (99%), 392 (99%) and 390 (100%) of patients in the PBO + MTX, CZP 200 mg and CZP 400 mg q2w + MTX. The most common concomitant medications at Baseline, other than MTX as background medication (pre-specified), were folic acid, diclofencac, methylprednisolone and prednisone. See **Table 23** and **24**. Sulfasalazine and hydroxychloroquine were other DMARDs commonly used by patients across the treatment groups.

Table 23. Concurrent Mediations at Baseline – Study 027

Concurrent Medications at Baseline Taken by ≥ 10% of Patients - Study 027 (ITT Population)				
Medication [a]	PBO + MTX N = 199	CZP 200 sc q2w+MTX N = 392	CZP 400 sc q2w+MTX N = 389	Overall N = 980
# of Patients with ≥ 1 concurrent medication at Baseline	198 (99.5%)	391 (99.5)	389 (99.7%)	978 (99.6%)
Methotrexate	198	391	389	978
Folic Acid	136 (68%)	277 (68%)	265 (68%)	678 (69%)
Diclofenac	58 (29%)	103 (26%)	103 (26%)	264 (27%)
Methylprednisolone (derm.)	48 (24%)	76 (19%)	82 (21%)	206 (21%)
Prednisone	46 (23%)	93 (24%)	82 (21%)	221 (23%)
Methylprednisolone (systemic hormonal prep., excl. sex)	39 (20%)	63 (16%)	72 (19%)	174 (18%)
Meloxicam	26 (13%)	55 (14%)	55 14%)	136 (14%)
Prednisolone	14 (7%)	51 (13%)	53 (14%)	118 (12%)
Nimesulide	20 (10%)	46 (12%)	46 (12%)	112 (11%)
Omeprazole	21 (11%)	46 (12%)	43 (11%)	110 (11%)
Enalapril (CV)	19 (10%)	45 (12%)	38 (10%)	102 (10%)

(a.) Medications coded in more than 1 WHODRUG Anatomical Group. Abbreviations: prep. = preparation; excl.=excluding; CV=cardiovascular; GU=genitourinary; horm.=hormone; tr.=tract.; derm.=dermatology.
Revised from sponsor Table 11:7, page 96 of 8823.

Table 24 Non-Biologic DMARD Medication at Baseline– Study 027

Past Nonbiological DMARD Medication - Study 027 (ITT Population)				
Medication	PBO + MTX N = 199	CZP 200 sc q2w + MTX N = 393	CZP 400 sc q2w + MTX N = 390	Overall N = 982
# Pts. with ≥ 1 past DMARD	199 (100%)	393 (100%)	390 (100%)	982 (100%)
Methotrexate[a]	198	392	390	980
Sulfasalazine	63 (32%)	124 (32%)	123 (32%)	310 (32%)
Hydroxychloroquine	59 (30%)	89 (23%)	90 (23%)	238 (24%)
Leflunomide	36 (18%)	67 (17%)	65 (17%)	168 (17%)
Sodium aurothiomalate	17 *9%)	35 (9%)	34 (9%)	86 (9%)
Gold	12 (6%)	19 (5%)	17 (4%)	48 (5%)
d-Penicillamine	4 (2%)	6 (2%)	7 (2%)	17 (2%)
Aurothioglucose	2 (1%)	1 (0%)	5 (1%)	8 (1%)
Cyclophosphamide	2 (1%)	6 (2%)	4 (1%)	12 (1%)
Ciclosporin	9 (5%)	14 (4%)	20 (5%)	43 (5%)
Azathioprine	11 (6%)	18 (5%)	16 (4%)	45 (5%)
Auranofin	3 (2%)	3 (1%)	2 (1%)	8 (1%)
Aurotioprol	0	2 (1%)	2 (1%)	4 (0%)
Reumacon	0	1 (0%)	0	1 (0%)
(a.) 2 pts. shown as not taking MTX from the Ukraine site. Databse does not have information.				
Revised from sponsor Table 11:9, page 10 of 8823.				

TNF Inhibitors and Other Biological Medications – Study 027

The number of patients who had previously received an anti-TNF-inhibitor or another therapeutic biologic product for RA (**Table 25**) was small in each of the three treatment groups. The eligibility criteria in Study 027 excluded patients who had received any biologic therapeutic agent for RA within 6 months prior to Baseline. See Section 5.3 Discussion of Individual Studies.

Table 25. Past TNF or Other Therapeutic Biologic Medication for RA – Study 027

Past Anti-TNF or Other Biological Medication for RA - Study 027 (ITT Population)				
Medication	PBO + MTX N = 199	CZP 200 mg sq q2w + MTX N = 393	CZP 400 mg sc q2w + MTX N = 390	Overall N = 982
# Patients with ≥ 1 past anti-TNF or other biolotical medication	7 (4%	11 (3%)	16 (4%)	34 (4%)
Infliximab	4 (2%)	6 (2%)	12 (3%)	22 (2%)
Etanercept	4 (2%)	3 91%)	3 (1%)	10 (1%)
Natalizumab	1 (1%)	0	2 (1%)	3 (0%)
Rituximab	0	0	1 (0%)	1 (0%)
Adalimumab	0	2 (1%)	0	2 (0%)
Anakinra	0	1 (0%)	0	1 (0%)
Revised from sponsor Table 11:10, page 101 of 8823.				

Rescue Medication – Study 027

Rescue medication was used by 11%, 10% and 13% of the patients in the PBO + MTX, CZP 200 mg and 400 mg q2w + MTX treatment groups, respectively. Rescue medication was pre specified in the protocol as medication used for treatment of RA other than the permitted concomitant medications: oral corticosteroids (< 10mg prednisone or equivalent per day), NSAIDS/selective COX-2 inhibitors, analgesics, intra-articular or intra-muscular injections of corticosteroids (< 80 mg methylprednisolone per injection) and MTX (< the entry dose).

Health Outcomes Assessments at Baseline
The Baseline scores in the SF-36, PCS and MCS, and the 8 domains, were similar across the three treatment groups. The MCS scores were higher compared to the PCS scores, consistent with what has been reported in the literature for the general RA population. See **Table 26.** Overall, the balance in the PCS and MCS scores demonstrated that patients experienced a comparable impact of their disease on health-related quality of life.

Table 26. Baseline SF-36 Scores – Study 027

SF-36 Baseline Scores - Study 027 (ITT Population)			
SF-36	PBO + MTX N = 199	CZP 200 mg sc q2w + MTX N =393	CZP 400 mg sc q2w + MTX N =393
PCS			
Mean (SD)	31 (6)	31 (7)	31 (7)
Median (min, max)	31 (15, 54)	31 (12, 57)	30 (15, 59)
MCS			
Mean (SD)	39 (11)	40 (11)	39 (11)
Median (min, max)	37 (15, 69)	38 (16, 70)	38 (15, 73)

Abbreviations: MTX=methotrexate; N= number of patients in group. Revised sponsor Table 11.6, page 94 of 8823.

6.1.4 Analysis of Primary Endpoint(s) – Study 027

The pivotal Phase 3 Study 027 was a 52-week, randomized, placebo-controlled trial designed to evaluate CZP in patients with active RA who have an incomplete response to MTX. Study 027 employed the lyophilized formulation which is not the intended formulation for the commercial market. One co-primary efficacy endpoint was the percentage of patients who achieved an ACR20 response at Week 24 and the second co-primary efficacy endpoint was the change from Baseline in the mTSS at week 52. The protocol also specified two key secondary endpoints, major clinical response defined as the ACR70 response at any two time-points 24 weeks apart during the study and at all assessments in-between (ITT population) and the sustained response defined as ACR20 at both weeks 24 and 52.

Statistically significant and clinically meaningful efficacy was demonstrated by the ACR20 response at Week 24, 59% and 61% in the CZP 200 mg and 400 mg sc q2w + MTX groups, respectively, compared with 14% in the PBO group ($p<0.001$ for both active treatment groups). A total of 53% and 55% of patients, treated with CZP 200 mg and 400 mg sc q2w + MTX, respectively, achieved an ACR20 response at Week 52 compared to 13% in the PBO + MTX treatment group ($p<0.001$). The small differences between the two CZP treatment groups were neither statistically significant nor clinically meaningful. Overall, these results demonstrated that efficacy measured by the ACR response at week 24 was maintained over time. See **Table 27.**

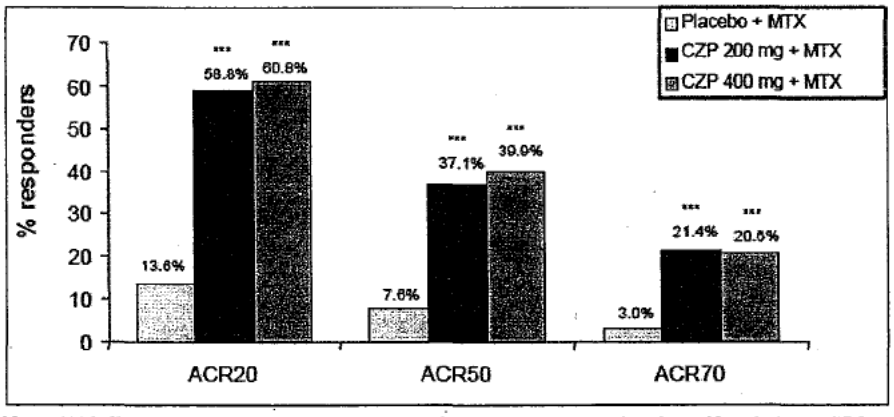
A higher percentage of patients in the two active treatment groups achieved ACR50 and ACR70 response than did patients in the PBO + MTX group at Week 24. The pre-specified odds ratio versus PBO control was statistically significantly ($p<0.001$) greater than 1.0 in both active groups for each of these endpoints. See **Table 27** and **Figure 5.**

Table 27. Co-Primary ACR20 Response at Week 24 and Week 52 – Study 027

ACR Response - Study 027 (ITT Population)	PBO+ MTX N = 199	CZP 200 sc q2w + MTX N = 383	CZP 400 sc q2w + MTX N = 390
ACR-20			
Week 24			
n [c.]	198	388	388
Responder	27 (14%)	288 (59%)	236 (61%)
Odds ratio vs PBP+MTX [a.] (97.5% CI)		9 (5, 16)	10 (6, 17)
p-value		<0.001	<0.001
Week 52			
n [c.]	198	392	388
Responder	26 (13%)	208 (53%)	213 (55%)
Odds ratio vs PBO+MTX (95% CI) [b.]		8 (5, 12)	8 (5, 13)
ACR-50			
Week 24			
Responder	15 (8%)	144 (37%)	155 (40%)
Odds ratio vs PBO+MTX (95%CI) [b.]		8 (4, 13)	9 (5, 15)
p-value		<0.001	<0.001
Week 52			
Responder	15 (8%)	149 (38%)	155 (40%)
Odds ratio vs PBO+MTX (95%CI) [b.]		8 (4, 14)	8 (5, 5)
ACR-70			
Week 24			
Responder	6 (3%)	83 (21%)	80 (21%)
Odds ratio vs PBO+MTX (95%CI) [b.]		9 (3, 22)	8.7 (4, 21)
p-value		<0.001	<0.001
Week 52			
Responder	7 (4%)	83 (21%)	90 (23%)
Odds ratio vs PBO+MTX (95%CI) [b.]		8 (3, 17)	9 (4, 9)
p-value		<0.001	<0.001

Abbreviations: MTX=methotrexate; CI=confidence interval; PBO=placebo.
(a.) Odds ratio: CZP/PBO calculated using logistic regression with factors for treatment and region.
(b.) Wald p-values for the comparison of the treatment groups were calculated using logistic regression with factors for treatment and region.
(c.) n remains the same for calculation of the ACR-50 responses at Week 24 and Week 52, respectively.
Note: patients who withdrew or used rescue medication were considered as non-responders from that time-point forward. Revised from sponsor Table 11:11, page 105 of 8823.

Figure 5. ACR 20/50/70 Response at Week 24 – Study 027



Notes: *** indicates p <0.001. P-values for comparison of treatment groups were based on odds ratio (versus PBO + MTX) rather than percent responders. Patient numbers by treatment group: Placebo + MTX (N=199; n=198), CZP 200 mg + MTX (N=393; n=388), CZP 400 mg + MTX (N=390; n=388). N=Number of patients in treatment group; n=Number of patients with non-missing response.

Sponsor Source Tables 14.2.1:1; Table 14.2.6:1, Table 14.2.6:3.

Sensitivity Analyses

ACR20 Responder Rate at Week 24 – Study 027

All the pre-specified sensitivity analyses at week 24 supported the primary efficacy analyses in Study 027. These pre-specified sensitivity analyses for the co-primary efficacy endpoint, ACR20 response at week 24, were based on the ITT population and included specific imputation rules techniques, LOCF approach and multiple imputation analysis. The first sensitivity analysis used the following algorithm: patients withdrawing before Week 16, regardless of their final outcomes, were considered as ACR20 non-responders at Week 24. Patients who dropped out at or after Week 16 but before Week 24, and were ACR20 non-responders at the time of withdrawal, were considered ACR20 non-responders at Week 24. The remaining PBO patients who withdrew from the study at or after Week 16 but before Week 24 were considered as ACR20 responders at Week 24 if they were ACR20 responders at the time of withdrawal. The remaining patients assigned to treatment with CZP were considered as ACR20 responders at Week 24 if the withdrawals occurred at or after Week 16 but before Week 24 and if they were ACR20 responders at the time of withdrawal. The remaining CZP patients who dropped out of the study at or after Week 16 but before Week 24 were considered ACR20 non-responders at Week 24 if they did not satisfy the above criteria.

The second sensitivity analysis was the last (post-Baseline) observation carried forward (LOCF) analysis. Missing values were imputed by carrying forward the last efficacy measurement. The third sensitivity analysis used the multiple imputation technique over time with the logistic model. See **Table 28.**

Table 28. ACR20 Responder Rate at Week 24 – Study 027 (ITT Population)

ACR-20 Responder Rate at Week 24 - Sensitivity Analyses - Study 027			
	PBO + MTX N = 199	CZP 200 mg sc q2w + MTX N = 393	CZP 400 mg sc q2w + MTX N = 390
Last Observation Carried forward (LOCF) (ITT Population)			
n	196	391	385
Responder	39 (20%)	269 (69%)	269 (70%)
Non-responder	157 (80%)	122(31%)	116 (30%)
Odds ratio vs PBO + MTX [a]		9	10
97.5% CI for odds ratio		[6, 15]	[6, 16]
p-value [c]			
Odds ratio vs 200 mg sc q2w + MTX			1
95% CI for odds ratio			[1, 1]
p-value [c]			0.8
Multiple Imputation (ITT Population)			
n	196	391	387
Responder	52 (27%)	281 (72%)	292 (76%)
Non-responder	144 (74%)	110 (28%)	95 (25%)
Odds ratio vs PBO + MTX		7	7
97.5% CI for odds ratio		[4, 10]	[5, 11]
p-value [c]		<0.001	<0.001
Odds ratio vs 200 mg sc q2w + MTX			1
95% CI for odds ratio			[1, 2]
p-value [c]			0.62

(a.) Odds ratio: CZP/PBO calculated using logistic regression with factors for treatment and region.
(b.) Odds ratio: CZP 400 mg sc q2w + MTX/ CZP 200 mg sc q2w+MTX calculated using the MI based on logistic regression with factors for treatment and region.
(c.) MI based p-values for the comparison of the treatment groups was calculated using MI based logistic regression with factors for treatment and region.
Abbreviations: MI=multiple imputation.
Revised from sponsor Tables 14.2.1:3 through 14.2.1:5, pages 1269 -1271 of 8823.

Co-Primary Efficacy Endpoint – Study 027
Inhibition of Progression of Structural Damage

The co-primary efficacy endpoint, inhibition of progression of structural damage, was assessed by the change in modified Total Sharp Score (mTSS) from Baseline to Week 52 and was statistically significantly decreased in the CZP 200 mg and 400 mg q2w + MTX groups compared to PBO + MTX ($p<0.001$). The difference between the two CZP treatment groups was not significant ($p > 0.05$). See below for the radiographic results at Week 24, a key secondary efficacy outcome. See **Table 29.**

The mTSS score at Week 52 for the early withdrawal patients was pre-specified to be imputed by linear extrapolation of the scores from the radiographs taken at the early Withdrawal visit. The radiographic claims in Study 027 were based on the difference in radiographic scores in films taken at 6 months and at 12 months. For all responder analyses, it was pre-specified that patients who withdrew for any reason or used rescue medication were considered as non-responders from that time-point onwards, unless stated otherwise. The method of analysis involved ranking these data and then analyzing those ranks using ANCOVA.

Patients who withdrew before Week 52 and had radiographs taken at their early withdrawal visit were included in this analysis. The mTSS at Week 52 for these early withdrawal patients was estimated using linear extrapolation of the scores from the radiographs taken from the early Withdrawal visit. If this was not performed, the Week 24 score was used where possible. Those patients with no post-Baseline visit were not included in the analysis. Missing scores at Baseline were imputed by the median scores of all the randomized patients who had Baseline scores. The Baseline x-ray was the x-ray collected at the Baseline visit or within 42 days after the Baseline visit. For post Baseline x-rays, a window of ± 30 days was applied in case a repeat x-ray was required if the original was of poor quality. If the additional x-ray was not collected within the window, the original x-ray was used. Out-of-window data were treated as missing.

In order to gauge the magnitude of the effect of CZP, we examined the pre-specified analysis of the percent inhibition of mTSS using the mean change from Baseline in mTSS for the CZP treatment groups compared to the PBO + MTX groups at Week 24 and 52. The percent inhibition from Baseline to week 24 was 87% and 83% with CZP 200 mg and 400 mg sc q2w + MTX treatment, respectively, and, at Week 52 was 85% and 92% inhibition with CZP 200 mg and 400 mg sc q2w + MTX treatment, respectively. See **Table 29.**

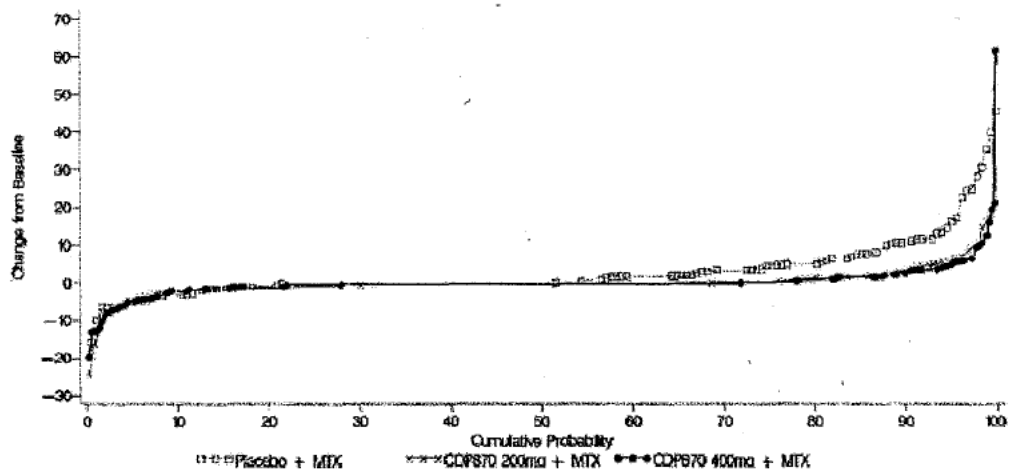
These results show a significant inhibition of progression of structural damage with both CZP doses at both Week 24 and Week 52. This level of inhibition exceeds the 75% level of inhibition that the Agency has used to distinguish highly effective agents that "inhibit" from less effective agents that are described as "slowing radiographic progression".

Table 29. Change from Baseline in mTSS at Weeks 24 and Week 52 – Study 027

Comparrison of Change from Baseline in mTSS at 52 Weeks Linear Extrapolation - ITT Population			
	PBO+MTX N = 199	CZP 200 mg sc q2w + MTX N = 393	CZP 400 mg sc q2w + MTX N = 390
Baseline mTSS			
n	199	391	389
Mean (SD)	39 (45)	38 (49)	38 (47)
Change from Baseline at Week 24			
n	180	353	355
Mean (SD)	1.3 (4)	0.2 (3)	0.2 (4)
Difference [a.] vs PBO + MTX (b.)		-0.5	-0.5
95% CI for Difference		[0.8, 0]	[-0.7,0]
p-value [c.]		<0.001	<0.001
% inhibition vs PBO+MTX [d.]		87%	83%
Change from Baseline at Week 52			
n	181	364	363
Mean (SD)	2.8 (8)	0.4 (6)	0.2 (5)
Difference [a.] vs PBO+MTX [b.]		-0.5	-0.6
97.5% CI for Difference		[-1.5, 0]	[-1.5,0]
p-value [c.]		<0.001	<0.001
% Inhibition vs PBO + MTX [d.]		85%	92%
Difference [a.] vs CZP 200 mg+MTX			0
95% CI for Difference			[0,0]
p-value [c.]			0.89
(a.) The differences are between CZP200/400 mg +MTX minus PBO+MTX. (b.) Hodges-Lehman point estimate of shift and CI. (c.) ANCOVA on the ranks with region and treatmetn as factors and rank Baseline as a covariate. Abbreviations: SD=standard deviation; PBO=placebo; MTX=methotrexate; CI=confidence interval. Revised from Table 11:14, page 118 of 8823 and Table 14.2.2:1, page 1360 of 8823.			

Cumulative probability plots are useful for displaying the distribution of values for radiographic progression and comparing results between study arms. A cumulative distribution plot for Study 027 is shown in **Figure 6.** From the cumulative probability plot, the proportion of patients exhibiting a value less than or equal to the values of change in the mTSS from Baseline on the y-axis can be read on the x-axis. The cumulative probability plot demonstrates that for any positive value of radiographic progression, the likelihood of progression was greater for the PBO + MTX group than for the both the CZP groups. In Study 050, the CZP 400 mg dose regimen appears to be more effective for preventing radiographic progression than does the CZP 200 mg dose regimen with extended treatment. In Study 027, there was no evidence for a difference between dose regimens for inhibition of progression of structural damage.

Figure 6. Cumulative Probability Plot: Change from Baseline in mTSS at Week 52 – Linear Extrapolation – Study 027 (ITT Population), Sponsor Figure 14.2.7:104) page 2733 of 8823



Change from Baseline in the Erosion Score and Joint Space Narrowing Score – Study 027
The changes from Baseline in the erosion score was statistically significantly ($p<0.001$) smaller in both CZP 200 mg and 400 mg sc q2w + MTX groups compared to the PBO + MTX group at Week 24 and at Week 52. The change from Baseline in joint space narrowing scores was statistically significantly ($p< 0.01$) smaller in both the CZP + MTX groups compared with the PBO + MTX group at Week 24 and Week 52. See **Table 30.**

Table 30. Change from Baseline: Erosion and Joint Space Narrowing Scores, Week 24 and 52 - Study 027

Change from Baseline in Erosion Score and in Joint Space Narrowing Score at Week 24 and at Week 52			
	PBO+ MTX	CZP 200 sc q2w + MTX	CZP 400 sc q2w + MTX
	N= 199	N=393	N=390
Erosion Score			
Baseline			
n	199	391	389
Mean (SD)	14 (21)	15 (24)	14 (23)
Change from Baseline at Week 24			
n	180	353	355
Mean (SD)	0.7 (2)	0 (2)	0.1 (2)
Difference [a.] vs PBO +MTX [b.]		0	0
95% CI for Difference [c.]		[-0.5, 0]	[-0.5, 0]
p-valve		<0.001	<0.001
Change from Baseline at Week 52			
n	181	364	363
Mean (SD)	1.5 (4)	0.1 (3)	0 (3)
Difference [a.] vs PBO+MTX [b.]		0	0
95% CI for Difference [c.]		[-0.5, 0]	[-0.5, 0]
p-value		<0.001	<0.001
Joint Space Narrowing Score			
Baseline			
n	199	391	389
Mean (SD)	25 (27)	24 (28)	24 (27)
Change from Baseline at Week 24			
n	180	355	355
Mean (SD)	0.7 (2)	0.2 (3)	0.2 (2)
Difference (a.) vs PBO+MTX [b.]		0	0
95% CI for Difference [c.]		[0, 0]	[0, 0]
p-value		0.008	0.008
Change from Baseline at Week 52			
n	181	367	363
Mean (SD)	1.4 (5)	0.4 (4)	0.2 (3)
Difference [a.] vs PBO+MTX [b.]		0	0
95% CI for Difference [c.]		[0, 0]	[0, 0]
p-value		0.006	0.003

(a.) The differences between CZP 200 mg/400 mg +MTX minus PBO+MTX.
(b.) Hodges-Lehman point estimates of the shift and CI.
(c.) ANCOVA on the ranks with region and treatment as factors and rank Baseline as a covariate. Abbreviations: CI=confidence interval; PBO=placebo' MTX= methotrexate; SD=standard deviation. Revised from sponsor Table 11:15, page 122 of 8823.

Sensitivity Analyses - mTSS at Week 52 – Study 027

Table 31 summarizes the missing and non-missing data from analysis of change from Baseline in mTSS at 52 Weeks (ITT population). These data clarify why the (n) in the different analyses do not represent the total ITT population. There were very few patients in the ITT population who had no x-ray data at all.

The protocol specified two sensitivity analyses. The first examined the ratio of week 52 radiographic scores to baseline scores (**Table 32**) using log-transformed data. The second (**Table**

33) analyzed the primary radiographic endpoint using the LOCF instead of linear extrapolation for missing data. Both sensitivity analyses supported the primary analysis.

Table 31. Summary of Missing Data and Non-Missing Data from Analysis of Change from Baseline in mTSS at Week 52 and Week 24

Summary of Missing Data and Non-Missing Data from Analysis of Change from Baseline in mTSS at **Week 52, Study 027** (ITT Population)			
Treatment	PBO + MTX N = 199	CZP 200 mg + MTX N = 393	CZP 400 mg + MTX N = 390
Pts. w/observed data	42	248	268
Pts. with B/L and at least one B/L	181	364	363
Pts. without extrapolation	18	27	26
Pts. with no usable x-ray data	0	2	1
Pts. with missing B/L	2	8	5
Summary of Missing Data and Non-Missing Data from Analysis of Change from Baseline in mTSS at **Week 24, Study 027** (ITT Population)			
Pts. with observed data	44	254	278
Pts. with B/L and at least one B/L	180	353	355
Pts. without extrapolation	19	38	34
Pts. with no usable x-ray data	0	2	1
Pts. with missing B/L	2	8	5

Revised from sponsor Table 42 and 43 (Information Request response July 18, 2008)

Table 32. Comparison of the Ratio to Baseline in mTSS at Week 52: Linear Regression

Comparison, Ratio to Baseline in mTSS at Week 52 - Linear Extrapolation - Log Transformed Data (ITT)			
Treatment	PBO + MTX N = 199	CZP 200 mg sc q2w + MTX N =393	CZP 400 mg sc q2w + MTX N = 393
n	172	345	352
Adj. Geometric Mean	1.08	1.02	1.02
Ratio vs PBO+MTX [a]			
Adj. Geometric Mean [97.5% CI]		0.94 [0.89, 1]	0.94 [0.89, 1]
p-value		0.017	0.018
Percent Reduct [97.5% CI] [c]		5.9 [0.4, 11]	5.8 [0.3, 11]
Ratio (d.) vs CZP 200mg+MTX [a]			
Adj. Geometric Mean [95% CI]			1.00 [0.9, 1]
p-value			0.968
Percent Reduct [95% CI] [c]			Minus 1 [-4.2, 4]

(a) ANCOVA on log transformed data with region and treatment as factors and baseline as a covariate.
(b) The ratios presented are 'CDP870 200mg/400mg + MTX over PBO + MTX'.
(c) Percent Reduction = 100 x [1 - ratio 'CDP870 200mg/400mg + MTX over PBO + MTX'].
(d) The ratio presented is 'CDP870 400mg + MTX over CDP870 200mg + MTX'.
(e) Percent Reduction = 100 x [1 - ratio 'CDP870 400mg + MTX over CDP870 200mg + MTX']. Revised from sponsor Table 14.2.2:3, page 1364 of 8823

Table 33. Comparison of the Change from Baseline in mTSS at Week 52 - LOCF

Comparison of the Change from Baseline in mTSS at Week 52 - LOCF (ITT)			
Treatment	PBO + MTX N = 199	CZP 200 mg sc q2w + MTX N =393	CZP 400 mg sc q2w + MTX N = 393
n	181	364	363
Mean (SD)	1.1 (3)	0.1 (3.2)	0.2 (4.1)
Median (Q1, Q3)	0 (0, 1.5)	0 (minus 0.5, 0.5)	0 (minus 0.5, 0.5)
Min, Max	Minus 5, 15	Minus 17, 29	Minus 20, 62
Diff (a) vs PBO+MTX [c.]		Minus 0.5	Minus 0.5
97.5% CI for Diff [c.]		[Minus 0.5, 0]	[Minus 0.5, 0]
p-value [d.]		<0.001	<0.001
Diff. (b.) vs CZP 200mg+MTX [c.]			0
95% CI for Difference [c.]			[0, 0]
p-value [d.]			0.99

(a) The differences presented are 'CDP870 200mg/400mg + MTX minus PBO + MTX'.
(b) The difference presented is 'CDP870 400mg + MTX minus CDP870 200mg + MTX'.
(c) Hodges-Lehmann point estimate of shift and confidence interval (Proc StatXact)
(d) ANCOVA on the ranks with region, treatment as factors and rank baseline as a covariate.
Revised from sponsor Table 14.2.2:4, page 1366 of 8823

Two additional sensitivity analyses were completed at Week 52 and Week 24 (Study 027) as shown in **Tables 34** and **35**: 1) Change from baseline still missing after linear extrapolation at a specific time-point was imputed using the median of all valid observed changes from baseline at that time-point and 2) Change from baseline imputed for the post-baseline time-point, separately within treatment groups.

Table 34. Additional Sensitivity Analyses (mTSS) at Week 52 (ITT Population) Study 027

Comparison of the Change from Baseline in mTSS at Week 52 - Linear Extrapolation and Median Imputation of Change from Baseline by Baseline Quartile (ITT), Study 027			
Treatment	PBO + MTX N=199	CZP 200 mg + MTX N=393	CZP 400 mg + MTX N=390
n	199	391	390
Mean (SD)	2.6 (7.5)	0.4 (5.5)	0.2 (4.6)
Median	0 (-16, 46)	0 (-24, 62)	0 (-20, 62)
Difference [a.] vs PBO+MTX [c.]		-0.5	-0.5
[97.5%CI for Difference [c.]		[-1.0, 0.0]	[-1.0, 0.0]
p-value [d.]		<0.001	<0.001
Difference [b.] vs CZP 200 mg +MTX [c.]			0
[95%CI for Difference [c.]			[0.0, 0.0]
p-value [d.]			0.893
Comparison of the Change from Baseline in mTSS at Week 52 - Linear Extrapolation and Median Imputation of Change from Baseline by Baseline Quartile and Treatment Group (ITT), Study 027			
n	199	391	389
Mean (SD)	2.6 (7.5)	0.4 (5.5)	0.2 (4.6)
Median	0 (-16, 46)	0 (-24, 62)	0 (-20, 62)
Difference [a.] vs PBO+MTX [c.]		-0.5	-0.5
[97.5%CI for Difference [c.]		[-1.0, 0.0]	[-1.0, 0.0]
p-value [d.]		<0.001	<0.001
Difference [b.] vs CZP 200 mg +MTX [c.]			0
[95%CI for Difference [c.]			[0.0, 0.0]
p-value [d.]			0.887

Same footnotes as under **Table 35.**

Table 35. Additional Sensitivity Analyses (mTSS) at Week 24 (ITT Population) Study 027

Comparison of the Change from Baseline in mTSS at Week 24 - Linear Extrapolation and Median Imputation of Change from Baseline Quartile (ITT), Study 027			
Treatment	PBO + MTX N=199	CZP 200 mg + MTX N=393	CZP 400 mg + MTX N=390
n	199	391	389
Mean (SD)	1.2 (3.6)	0.2 (3.0)	0.2 (4.0)
Median	0 (-7, 21)	0 (-16, 29)	0 (-20, 62)
Difference [a.] vs PBO+MTX [c.]		0	0
[95%CI for Difference [c.]		[-0.5, 0.0]	[-0.5, 0.0]
p-value [d.]		<0.001	<0.001
Difference [b.] vs CZP 200 mg +MTX [c.]			0
[95%CI for Difference [c.]			[0.0, 0.0]
p-value [d.]			0.899
Comparison of the Change from Baseline in mTSS at Week 24 - Linear Extrapolation and Median Imputation of Change from Baseline by Baseline Quartile and Treatment Group (ITT), Study 027			
n	199	391	389
Mean (SD)	1.2 (3.6)	0.2 (3.0)	0.2 (4.0)
Median	0 (-7, 21)	0 (-16, 29)	0 (-20, 62)
Difference [a.] vs PBO+MTX [c.]		-0.3	-0.2
[95%CI for Difference [c.]		[-0.5, 0.0]	[-0.5, 0.0]
p-value [d.]		<0.001	<0.001
Difference [b.] vs CZP 200 mg +MTX [c.]			0
[95%CI for Difference [c.]			[0.0, 0.0]
p-value [d.]			0.893

(a) The differences presented are 'CDP870 200mg/400mg + MTX minus PBO + MTX'.
(b) The difference presented is 'CDP870 400mg + MTX minus CDP870 200mg + MTX'.
(c) Hodges-Lehmann point estimate of shift and confidence interval (Proc StatXact).
(d) ANCOVA on the ranks with region, treatment as factors and rank baseline as a covariate.

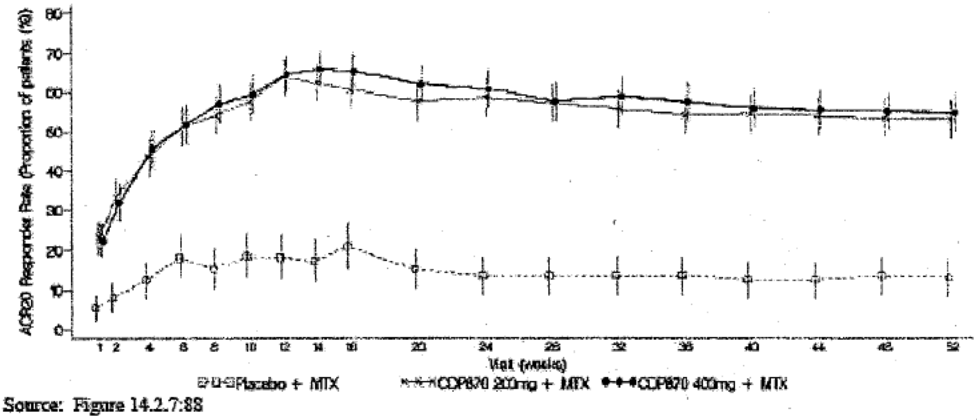
In summary, these results demonstrated statistically significant inhibition of the progression of structural damage, as measured by the mTSS, with both CZP dose regimens at Week 52 (co-primary endpoint) and at Week 24 (key secondary endpoint) in Study 027. These outcomes were supported by the major secondary efficacy endpoint inhibition of progression of structural damage in Study 050 at Week 24 and by the sensitivity analyses (027 and 050). In summary, both Study 027 and 050 support the proposed radiographic response claim for CZP in patients with RA.

6.1.5 Analysis of Secondary Endpoints(s) – Study 027

ACR20/50/70 Responses over Time by Visit – Study 027

The ACR 20 response in CZP 200 mg and 400 mg q2w + MTX groups demonstrated separation from the PBO + MTX group as early as the first week. The ACR20 response with both CZP dose regimens was maintained through Week 52 at each time-point (major secondary endpoint in Study 027). See **Figure 7** and see **Table 36.** Also see previous **Figure 5** for ACR50 and ACR70 responses.

Figure 7. ACR20 Responses by Visits Study 027 (ITT Population)



Source: Figure 14.2.7:88
Sponsor figure 11:2, page 108 of 8823

Table 36. Comparison of ACR20 Responder Rates by Visits – Study 027

Comparison of the ACR-20 Responder Rate by Visit - Study 027 (ITT Population)			
Visit	PBO + MTX N = 199	CZP 200 mg sc q2w + MTX N = 393	CZP 400 mg sc q2w + MTX N =390
Week 1			
n	196	385	381
Responder	11 (6%)	88 (23%)	85 (22%)
Non-responder	185 (94%)	297 (77%)	296 (78%)
Odds ratio vs PBO+MTX [a.]		5.4	5.1
95% CI for odds ratio		[3, 11]	[3, 10]
p-value [c.]		<0.001	<0.001
Odds ratio vs CZP 200mg +MTX [b.]			1
95% CI for odds ratio			[1, 1]
p-value [c.]			0.8
Week 6			
n	198	390	385
Responder	36 (18%)	200 (51%)	200 (52%)
Non-responder	162 (82%)	190 (49%)	185 (48%)
Odds ratio vs PBO+MTX [a.]		5	5
95% CI for odds ratio		[3, 8]	[3, 8]
p-value [c.]		<0.001	<0.001
Odds ratio vs CZP 200mg +MTX [b.]			1
95% CI for odds ratio			[1, 1]
p-value [c.]			1
Week 12			
n	197	389	387
Responder	36 (18%)	248 (64%)	250 (65%)
Non-responder	161 (82%)	141 (36%)	137 (35%)
Odds ratio vs PBO+MTX [a.]		8	8
95% CI for odds ratio		[5, 12]	[5, 13]
p-value [c.]		<0.001	<0.001
Odds ratio vs CZP 200mg +MTX [b.]			1
95% CI for odds ratio			[1, 1]
p-value [c.]			1
Week 24			
n	198	388	388
Responder	27 (14%)	228 (59%)	236 (61%)
Non-responder	171 (86%)	160 (41%)	152 (40%)
Odds ratio vs PBO+MTX [a.]		9	10
95% CI for odds ratio		[6, 15]	[6, 16]
p-value [c.]		<0.001	<0.001
Odds ratio vs CZP 200mg +MTX [b.]			1
95% CI for odds ratio			[1, 1]
p-value [c.]			1

(a.) Odds ratio: CZP/PBO+MTX calculated using logistic regression with factors for treatment and region; (b.) Odds ratio: CZP 400 mg/CZP 200 mg calcualted using logistic regression with factors for treatment and region; (c.) Wald p-values for the comparison of treatment groups were caluclated using logistic regression factors for treatment and region.
Revised from sponsor Table 14.2.7:1, pages 1487-1522.

Sustained Clinical Response – Study 027

A key secondary efficacy endpoint, a sustained clinical response, was pre-specified and defined as an ACR20 response at both Week 24 and 52. Both CZP treatment groups showed a statistically significantly higher proportion of patients meeting this definition compared to the PBO + MTX group. See **Table 37.** The clinical response in Study 027 at week 24 showed no evidence of diminishing at Week 52. In summary, the sustained clinical response key secondary endpoint demonstrated maintenance of response out to one year.

Table 37. Sustained ACR20 Response at Both Week 24 and 52 – Study 027

Sustained ACR20 Response at Both Week 24 and 52 in Study 027 (ITT Population)			
	PBO + MTX N=199	CZP 200 mg q2w + MTX N=393	CZP 400 mg q2w + MTX N=390
n	198	392	368
Sustained Responders at Wk 24 and 52	23 (12%)	196 (50%)	197 (51%)
Responders at Wk 24 and Non-responder at Wk 52	4 (2%)	32 (8%)	39 (10%)
Non-responder at Wk 24 and Responder at Wk 52	3 (2%)	12 (3%)	16 (4%)
Non-responder at Wk 24 and at Wk 52	168 (85%)	148 (38%)	136 (35%)
Odds ratio vs PBO+MTX [a.]		8	8
95% CI for odds ratio		[5, 13]	[5, 13]
p-value [c.]		<0.001	<0.001
Odds ratio vs CZP 200 + MTX [b.]			1
95% CI for odds ratio			[1,1]
p-value [c.]			1
Treatment by region interaction [d.]	p-value = 0		

(a.) Odds ratio: CZP+MTX calculated using logistic regression with factors for treatment and region.
(b.) Odds ratio: CZP 400mg/CZP 200mg calculated using logistic regression with factors for treatment and region.
(c.) Wald p-value has been calculated using logistic regression with treatment and region and treatment by region interaction as factors. Revised fom sponsor Table 14.2.8:1, page 2739 of 8823.

Major Clinical Response – Study 027

The key secondary efficacy endpoint, major clinical response, was pre-specified as being an ACR70 responder at any two time-points 24 weeks apart during the study and at all assessments in between. A larger proportion of patients in both active treatment groups achieved a major clinical response compared to the PBO + MTX group and the pre-specified odds ratio for achieving a major clinical response versus PBO+MTX was statistically significantly greater than 1 ($p<0.001$). See **Table 38.**

Table 38. Major Clinical Response – Study 027

Major Clinical Response - Study 027 (ITT Population) ACR-70 responder, at any two time-points 24 weeks apart, during the study and at all assessments in-between.			
	PBO + MTX N = 199	CZP 200 mg sc q2w+MTX N = 393	CZP 400 mg sc q2w + MTX N = 390
n	198	392	386
Responder	2 (1%)	49 (13%)	49 (13%)
Odds ratio vs PBO + MTX [a.]		15	15
95% CI for odds ratio [b.]		[4, 61]	[4, 62]
p-value		<0.001	<0.001

(a.) Odds ratio: CZP/PBO calculated using logistic regression with factors for treatment and region. (b.) Wald p-values for the comparison of the treatment groups were calculated using logistic regression with factors for treatment and region.
Revised from sponsor Table 14.2.7:87, page 2716 of 8823)

Change from Baseline in the ACR Components at Week 24 (LOCF) – Study 027

To assess whether the positive results on the ACR response was driven by a subset of components of the overall index, we examined the individual components of the ACR response. As shown in **Table 39**, all components of the ACR response showed improvement from baseline

in the CZP-treated patients. In addition, patients treated with CZP had greater improvement in the duration of morning stiffness and in the DAS28 compared to PBO-control patients.

Table 39. Percentage Change from Baseline –ACR Components – Study 027

Percentage Change from Baseline - ACR Components - Week 24 and 52 - Study 027 (LOCF - ITT Population)			
	PBO + MTX (N =199)	CZP 200 mg sc q2w + MTX (N= 393)	CZP 400 mg sc q2w + MTX (N= 390)
Tender Joint Count			
Baseline, Mean (SD)	30 (13)	31 (12)	31 (13)
% Change at Week 24, Median	-6	-70	-71
% Change at Week 52, Median	-5.6	-77	-79
Swollen Joint Count			
Baseline, Mean (SD)	21 (10)	22 (10)	22 (10)
% Change at Week 24, Median	-11	-76	-78
% Change at Week 52, Median	-10	-81	-85
Patient's Assessment of Pain - VAS			
Baseline, Mean (SD)	64 (20)	62 (20)	64 (17)
% Change at Week 24, Median	-8	-48	-50
% Change at Week 52, Median	-8	-53	-57
Patient's Global Assessment of Disease Activity			
Baseline, Mean (SD)	65 (20)	63 (20)	64 (18)
% Change at Week 24, Median	-8	-48	-52
% Change at Week 52, Median	-8	-55	-57
Physician's Global Assessment of Disease Activity			
Baseline, Mean (SD)	64 (17)	64 (15)	63 (15)
% Change at Week 24, Median	-13	-59	-60
% Change at Week 52, Median	-13	-63	-64
Health Assessment Quality - Disability Index			
Baseline, Mean (SD)	2 (1)	2 (1)	2 (1)
% Change at Week 24, Median	-6	-33	-35
% Change at Week 52, Median	-6	-33	-36

Table 39. Continued

Percentage Change from Baseline - ACR Components - Week 24 and 52 - Study 027 (LOCF - ITT Population)			
	PBO + MTX N =199	CZP 200 mg sc q2w + MTX (N=393)	CZP 400 mg sc q2w + MTX (N=390)
Duration of Morning Stiffness			
Baseline, Mean (SD)	3 (4)	3 (4)	2 (3)
% Change at Week 24 Median	-33	-75	-75
% Change at Week 52, Median	-33	-80	-87
DAS28(ESR)			
Baseline, Mean (SD)	7 (1)	7 (1)	7 (1)
% Change at Week 24, Median	-6	-35	-38
% Change at Week 52, Median	-6	-40	-41
Comparison Ratio to Baseline in CRP (LOCF-ITT Population)			
Week 24, Adj. Geometric Mean	0.9	0.4	0.4
95% CI	(0.7, 1)	(0.4, 0.5)	(0.4, 0.4)
Week 52, Adj. Geometric Mean	0.9	0.5	0.4
95% CI	(1, 1)	(0.4, 0.5)	(0.4, 0.5)
Ratio to Baseline ESR (LOCF-ITT Population)			
Week 24, Median	0.83	0.57	0.51
Week 52, Median	0.83	0.58	0.55

Revised from sponsor Table 14.2.7:13, pages 1696 to 1704 of 8823;Table 14.2.7:19, pages 1775 to 1778 of 8823;Table 14.2.7:25, pages 1854 to 1861 of 8823;Table 14.2.7:25, pages 1854 to 1861 of 8823; Table 14.2.7:31, pages 1946 to 1953 of 8823; Table 14.2.7:37, pages 2038 to 2045 of 8823; Table 14.2.7:43, pages 2116 to 2119 of 8823; Table 14.2.7:49, pages 2190 to 2193 of 8823; Table 14.2.7:55, pages 2264 to 2267; Table 14.2.7:61, page 2343 to 2361 of 8823; Table 14.2.7:64, pages 2385 to 2388 of 8823. Abbreviations: mITT= modified intent-to-treat population; SD=standard deviation; n= # patients that data was collected from in Study 027.

Health Assessment Questionnaire – Disability Index (HAQ-DI) – Study 027
The Health Assessment Questionnaire-Disability Index (HAQ-DI) is a well accepted measure of physical function in clinical trials of RA. Studies in RA patients have demonstrated that changes exceeding 0.22 units, on a scale of 0 – 3, are clinically meaningful. The HAQ-DI is a continuous endpoint that was pre-specified to be analyzed using the mean change from Baseline at Week 52 using an analysis of covariance (ANCOVA) model with region and treatment group as factors and Baseline value as a covariate. Missing values because of a patient withdrawal or data exclusion after the use of rescue medication were imputed by carrying forward the last efficacy measurement (LOCF imputation). Pending - statistics reviewer to complete a non-responder imputation for the HAQ-DI. See Statistic Review by Kate Meaker, PhD.

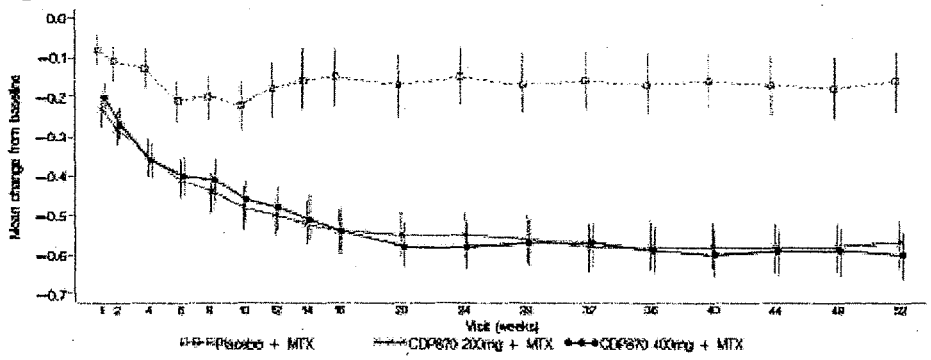
As shown in **Table 40**, patients in both CZP treatment groups demonstrated statistically significant and clinically meaningful improvement in physical function over PBO + MTX ($p<0.001$) at Week 25 and 52. The time-course of HAQ-DI responses (**Figure 8**) also demonstrated maintenance of response through to week 52.

Overall, the HAQ-DI results demonstrate that patients in the CZP treatment groups achieved statistically significant and clinically meaningful improvement in the HAQ-DI compared to the PBO treated patients.

Table 40 Health Assessment Questionnaire - Disability Index (HAQ-DI) - Study 027

Comparison of Change from Baseline in HAQ-DI - Study 027 Week 24 and Week 52 - LOCF (ITT Population)			
Visit Treatment	PBO+MTX N = 199	CZP 200 mg sc q2w + MTX N = 393	CZP 400 mg sc q2w + MTX N = 390
Week 24			
Baseline, Mean (SD)	1.7 (1)	1.7 (1)	1.7 (1)
Adj. Mean (SE)[a.]	-0.2 (0)	-0.6 (0)	-0.6 (0)
Diff[b.] vs PBO+MTX[a.]			
Adj. Mean [95%CI][c.]		-0.4 [-0.5, -0.3]	-0.4 [-0.5, -0.3]
P-value		<0.001	<0.001
Week 52			
Baseline, Mean (SD)	1.7 (1)	1.7 (1)	1.7 (1)
Adj. Mean (SE)[a.]	-0.2 (0)	-0.6 (0)	-0.6 (0)
Diff[b.] vs PBO+MTX[a.]			
Adj. Mean [95%CI][c.]		-0.4 [-0.5, -0.4]	-0.4 [-0.5, -0.4]
P-value		<0.001	<0.001
(a.) ANCOVA with region and treatment as factors and Baseline as covariate. (b.) The differences presented are CZP 200 mg/400 mg + MTX minus PBO+MTX. Abbbreviations: SE=standard error; CI=confidence interval; MTX=methotrexate; PBO=placebo. Revised from sponsor Table 11:16, page 125 of 8823 and Table 14.2.7:43, page 2116 of 8823.			

Figure 8. Change from Baseline in HAQ-DI by Visit – LOCF –ITT Population



Sponsor Figure 11:11, page 126 of 8823

Comparison of Change from Baseline in the SF-36 - Study 027

Patients in the CZP 200 mg and 400 mg q2w + MTX treatment groups demonstrated significant improvements in HRQoL compared to PBO + MTX, as assessed by the SF-36 (PCS and MCS scores and sub-domains). All the changes in scores were statistically significantly improved ($p<0.001$) following treatment at Week 24 and Week 52 in both CZP groups compared to the PBO + MTX group. See **Table 41.**

In the pre-specified sensitivity analyses (**Table 42**) comparison of the Change from Baseline in the SF-36 PCS and MCS scores at Week 24 and Week 52 - repeated analyses - direct likelihood), the mean scores in the CZP + MTX groups were statistically significantly higher than in the PBO + MTX group ($p<0.001$) in the PCS at both Week 24 and Week 52. The mean scores were not statistically significant in the MCS at either time-point (Week 24 and 52).

The results of the secondary efficacy endpoints, physical function and disability, as assessed by the HAQ-DI and supported by the SF-36 PCS and the sensitivity analyses, supported the proposed claim for improvement in physical function for CZP treated patients compared to PBO treated patients. The Agency has granted claims for improved physical function based on the HAQ-DI, with supportive SF-36/PCS outcomes in RA patients. The MCS does not provide adequate evidence to grant a claim in RA patients.

Table 41 Change from Baseline, SF-36 PCS and MCS - Study 027

Change from Baseline in SF-36 Physical and Mental Component - Study 027 Summary Scores at Weeks 24 and Weeks 52 (LOCF - ITT Population)			
	PBO+MTX N 199	CZP 200 mg sc q2w + MTX N =393	CZP 400 mg sc q2w + MTX N =390
Physical Component Summary (PCS)			
Baseline Mean (SD)	31 (6)	31 (7)	31 (7)
Change from Baseline at Week 24			
Adjusted Mean (SE) [a.]	2 (1)	8 (0)	8 (0)
Change from Baseline at Week 52			
Adjusted Mean (SE) [a.]	2 (1)	8 (0)	9 (0)
Mental Component Summary (MCS)			
Baseline Mean (SD)	39 (11)	40 (11)	39 (11)
Change from Baseline at Week 24			
Adjusted Mean (SE) [a.]	2 (1)	6 (1)	7 (1)
Change from Baseline at Week 52			
Adjusted Mean (SE) [a.]	2 (1)	6 (1)	6 (1)
p-value for all of the above components		*p<0.001*	*p<0.001*

(a.) ANCOVA with region and treatment as facotrs and Baseline as covariate.
Abbreviations: SE=standard error; MTX=methotrexate; PBO=placebo.
Revised from sponsor Table11:17, page 128 of 8823.

Table 42. Sensitivity Analysis for PCS and MCS – Study 027

Comparison of the Change from Baseline in SF-36 PCS and MCS Repeated Analysis (Direct Likelihood) (ITT Population) - Study 027			
	PBO + MTX N = 199	CZP 200 mg sc q2w + MTX N = 393	CZP 400 mg sc q2w + MTX N = 390
PCS at Week 24			
Adj. Mean (SE) (a.)	4 (1)	9 (0)	9 (1)
Diff. (b.) vs PBO+MTX [a.]			
Adj. Mean (SE) [95%CI]		4.5 [2, 7]	5 [3, 7]
p-value		<0.001	<0.001
PCS at Week 52			
Adj. Mean (SE) [a.]	5 (1.2)	9.2 (1)	10 (0.5)
Diff. (b.) vs PBO+MTX [a.]			
Adj. Mean (SE) [95%CI]		4 [2, 7]	5 [2, 7]
p-value		0.001	<0.001
MCS at Week 24			
Adj. Mean (SE) [a.]	7 (1)	8 (1)	7 (1)
Diff. (b.) vs PBO+MTX [a.]			
Adj. Mean (SE) [95%CI]		1 [-2, 4]	0 [-2, 1]
p-value		0.543	0.855
MCS at Week 52			
Adj. Mean (SE) [a.]	6 (2)	8 (1)	7 (1)
Diff. (b.) vs PBO+MTX [a.]			
Adj. Mean (SE) [95%CI]		2 [-1, 6]	1 [-2, 5]
p-value		0.173	0.459

(a.) Repeated analysis overtime with region, treatment and time as factors, and treatment by time interaction and baseline as covariate. (b.) The differences presented are CZP 200mg/ CZP 400mg + MTX minus PBO + MTX. Abbreviations: SE-std error; MTX=methotrexate; PBO=placebo; diff=difference; Revised from Table 14.5.1:2, pages 6699-6703 of 8823.

Assessment of Tiredness (Fatigue) – Study 027

Tiredness was measured with the Fatigue Assessment Scale (FAS), a numerical scale assessing tiredness, weariness as components of fatigue. [This scale has been tested in patients with sarcoidosis.] The SF-36 vitality domain was employed to support the FAS results. Patients in both CZP treatment groups had a statistically significant reduction in fatigue/tiredness assessed by the FAS at Weeks 12, 24 and 52 compared to PBO + MTX. (See **Table 43**) These results were supported by the SF-36 Vitality Domain at Week 12 to Week 52 compared to PBO + MTX ($p<0.001$ with LOCF and $p\leq 0.05$ with direct likelihood method).

Although both CZP treatment groups demonstrated statistically significantly greater reductions in fatigue/tiredness compared with the PBO + MTX treatment group, (b) (4)

The division requested a consult from the Study Endpoints and Label Development (SEALD) team to evaluate the adequacy of reduction in "Tiredness" as measured by weekly assessments in the Fatigue Assessment Scale (FAS) and monthly assessments with the SF-36 Vitality Domain, (b) (4). As fatigue is a multidimensional concept with physical, cognitive and emotional components, it remains unclear whether a single-term as was employed in the FAS can adequately represent the concept. From the literature, it has not been shown that patients with RA understand the concept similarly and whether the FAS instrument completely and appropriately captures this concept. The research study cited by the Patient Reported Outcome (PRO) dossier was a pilot study with 20 patients to assess the symptom of fatigue in RA. [1] (b) (4)

The SF-36 is a generic measure of overall health status for us in the general population and this instrument produces two summary scores, the Physical component Summary (PCS) and the mental Component summary (MCS). The SF-36 Vitality Domain was used as a measure of tiredness in addition to the FAS. Although the SF-36 has been widely used and translated into many languages, we did not find evidence to support use of the FAS in each of these multinational settings. Although there were statistically significant differences between treatment groups on the FAS, with replication in independent studies and supportive data were obtained from the SF-36 Vitality Domain, the magnitude of the treatment effect (active versus PBO) in the FAS was modest.

The division also requested a consult from SEALD for the PRO, Work Productivity Scale (WPS. There has not been validation of the additional secondary endpoint, Work Productivity Scale (WPS) in patients with RA. The WPS is not a measure of actual work productivity rather it asks patients questions about their perceived work productivity. The WPS is an instrument comprised of nine items that have not been shown to be clinically meaningful and valid measures of the multi-dimensional concept of "RA-related perceived work productivity.

(b) (4)

References:
1. Belza Tack, B Self-reported Fatigue in Rheumatoid Arthritis: A Pilot Study. Arthritis Care and Research. 1990;3(3) 154-157

Table 43. Comparison of Change from Baseline in FAS – Study 027

Comparison of Change from Baseline: Fatigue Assessment Score (FAS) Study 027			
LOCF (ITT Population)			
Timepoint	PBO + MTX N = 199	CZP 200 mg sc q2w + MTX N =393	CZP 400 mg sc q2w + MTX N = 390
Week 6			
Baseline, Mean (SD)	6.7 (2)	6.4 (2)	6.4 (2)
Adj. Mean (SE) [a.]	-0.8 (0.1)	-2 (0.1)	-2 (0.1)
Week 12			
Baseline, Mean (SD)	6.7 (2)	6.4 (2)	6.4 (2)
Adj. Mean (SE) [a.]	-0.6 (0.2)	-2.3 (0.1)	-2.2 (0.1)
Week 24			
Baseline, Mean (SD)	6.7 (2)	6.4 (2)	6.4 (2)
Adj. Mean (SE) [a.]	-0.9 (0.2)	-2.5 (0.1)	-2.5 (0.1)
Week 52			
Baseline, Mean (SD)	6.7 (2)	6.4 (2)	6.4 (2)
Adj. Mean (SE) [a.]	-0.8 (0.2)	-2.6 (0.1)	-2.5 (0.1)
p-value		*<0.001*	*<0.001*

(a.) ANCOVA with region and treatment as factors and Baseline as covariate.
Abbreviations: SE=standard error; MTX=methotrextae; PBO=placebo; CZP=CIMZIA.
Revised from sponsor Table 14.5.2:18, pages 7099 to 7108 of 8823.

Work Productivity Survey (WPS) – Study 027

The WPS assessed the impact of arthritis on a patient's productivity, within and outside the home, over the previous 4 weeks. As the WPS is not a measure of actual work productivity, rather, it asks patients questions about their perceived work productivity, [redacted] (b) (4) See the above comments from the SEALD consult discussed on page 90 of this review.

Additional Secondary Efficacy Measures – Study 027

Duration of Morning Stiffness – Study 027

The duration of morning stiffness (hours) was defined as the time elapsed between the time of usual awakening and the time the patient was a limber as he/she would be during a day involving typical daily activities. This secondary endpoint was among many other additional secondary endpoints in Study 027. Both CZP treatment groups demonstrated a statistically significant greater reduction in morning stiffness at each time point in the change from Baseline in the duration of morning stiffness (hours) compared to the PBO + MTX group ($p<0.001$). See **Table 44.**

Table 44. Comparison of the Change from Baseline in Duration of Morning Stiffness by Visit

Comparison of the Change from Baseline in Duration of Morning Stiffness by Visit (LOCF- ITT) - Study 027			
Visit	PBO + MTX N = 199	CZP 200 mg sc q2w + MTX N = 393	CZP 400 mg sc q2w + MTX N = 390
Week 1, Mean (SD)	-0.18 (2.9)	- 1.01 (2.8)	-0.73 (2.5)
Diff (b.) vs PBO+MTX [(a.)] Adj. Mean [95% CI]		-0.9 [-1.28, -0.5]	-0.7 [-1, -0.36]
Week 16, Mean (SD)	-0.82 (3.4)	-1.50 (3.3)	-1.58 (2.9)
Diff (b.) vs PBO+MTX [(a.)] Adj. Mean [95% CI]		-0.80 [-1.2, -0.42]	-1.06 [-1.4, -0.68]
Week 20, Mean (SD)	-0.73 (3.7)	-1.51 (3.3)	-1.69 (3.1)
Diff (b.) vs PBO+MTX [(a.)] Adj. Mean [95% CI]		-0.91 [-1.31, -0.51] <0.001	-1.28 [-1.68, -0.88] <0.001
Week 24, Mean (SD)	-0.76 (3.7)	-1.55 (3.3)	-1.70 (3.2)
Diff (b.) vs PBO+MTX [(a.)] Adj. Mean [95% CI]		-0.92 [-1.3, -0.53]	-1.26 [-1.66, -0.87]
Week 32, Mean (SD)	-0.99 (3.4)	-1.57 (3.3)	-1.74 (3.1)
Diff (b.) vs PBO+MTX [(a.)] Adj. Mean [95% CI]		-0.82 [-1.19, -0.44]	-1.18 [-1.55, -0.80]
Week 36, Mean (SD)	-0.89 (3.4)	-1.61 (3.4)	-1.75 (3.18)
Diff (b.) vs PBO+MTX [(a.)] Adj. Mean [95% CI]		-0.86 [-1.23, -0.49]	-1.19 [-1.56, -0.82]
Week 44, Mean (SD)	-0.91 (3.5)	-1.61 (3.4)	-1.74 (3.2)
Diff (b.) vs PBO+MTX [(a.)] Adj. Mean [95% CI]		-0.83 [-1.21, -0.46]	-1.16 [-1.54, -0.78]
Week 52, Mean (SD)	-0.91 (3.5)	-1.58 (3.3)	-1.78 (3.2)
Diff (b.) vs PBO+MTX [(a.)] Adj. Mean [95% CI]		-0.80 [-1.19, -0.42]	-1.19 [-1.58, -0.80]
p-value		*<0.001*	*<0.001*

Revised sponsor Table 14.2.7:50, page 2194 to 2204 of 8823.
(a) ANCOVA with region and treatment as factors and baseline as covariate.

Additional Secondary Efficacy Measures – Study 027

The DAS28(ESR), the DAS28(ESR) Remission, EULAR Response and the ESR were additional secondary endpoints employed to support the co-primary efficacy endpoint, the ACR responder criteria and each of these additional endpoints achieved a supportive outcome. The Time to withdraw Due to Lack of Efficacy, Euro Qol-5D Health State Evaluation and the Healthcare Resource Utilization Questionnaire each showed favorable outcome for the active treatment groups compared to the PBO + MTX group, therefore supporting the primary efficacy outcome. The Changes in RA Concomitant Medication did not show any significant differences across the treatment arms.

Changes in RA Concomitant Medication – Study 027

All patients in Study 027 were taking concomitant MTX at Baseline, as per the protocol. Overall, there were no significant changes in concomitant medication across the treatment groups.

Euro Qol-5D Health State Evaluation – Study 027

The EQ-5D was an exploratory endpoint only assessed in European patients. The patients in the CZP + MTX groups made the greatest improvements in the health state as assessed by the EQ-5D VAS with a change of mean score from 45.0 and 42.3 at Baseline for CZP 200 mg and CZP

400 mg q2w + MTX groups, respectively, to a mean score of 63 and 65 at Week 52, respectively, compared to PBO, with a mean score of 45 at Baseline and 48 at Week 52. The sensitivity analyses LOCF as a change from Baseline in EQ-5D health state (VAS) supported the primary efficacy outcome.

Healthcare Resource Utilization Questionnaire (HCRU) – Study 027
The HCRU questionnaire provided an assessment of healthcare resource utilization of the number and length of hospitalizations, outpatient and home health care visits, and the number of medical procedures. The Agency does not employ health care utilization data in support of the treatment of signs and symptoms of RA. Therefore, this endpoint was not used to support the proposed indication.

Subgroup Analysis of ACR20 Responder Rate at Week 24–Study 027
The CZP RA clinical development program was global in scope. In order to determine whether the treatment effect was consistent across different countries and subgroups, we examined responses by treatment arms in the various subgroups for the primary efficacy endpoint (ITT population). In general, responses were seen in CZP-treated patients in all subgroups, including patients in subsets by age, gender, race, disease duration and baseline corticosteroid use (**Table 45).**

Of note, anti-CZP antibody negative patients tended to have higher ACR20 response rates in both CZP 200 mg and 400 mg groups (60% and 61%, respectively) compared with anti-CZP antibody positive patients in both CZP 200 mg and 400 mg groups (48% and 50%, respectively).

In Study 027, in both CZP 200 mg and 400 mg + MTX groups, RF positive patients showed higher ACR20 responder rates, 62% and 62%, respectively, than did the RF negative patients, 48% and 55%, respectively. This trend has been observed with other TNF-inhibitors. Caution must be used in interpreting these data in Study 027 as the denominator was smaller in the RF negative patient population.

In summary, it appeared, irrespective of age, gender, race, weight, BMI, disease duration, MTX dose, corticosteroid use, that CZP treatment was associated with a clinical response as measured by the co-primary efficacy endpoint, ACR20 response at 24 weeks.

Table 45. Select ACR20 Subgroup Analyses – Study 027

Comparison of ACR20 Response, Select Subgroup Analyses - Study 027			
Subgroup	PBO + MTX N = 199	CZP 200 mg q2w + MTX, N = 393	CZP 400 mg q2w + MTX, N = 390
Age, < 65 years			
Responder	25 (15%)	194 (58%)	206 (62%)
Odds ratio vs PBO+MTX [b.]		8.023 [5.1, 13.2]	9.95 [6.2, 16.1]
Age, ≥ 65 years			
Responder	2 (8%)	34 (67%)	30 (52%)
Odds ratio vs PBO+MTX [b.]		NP	NP
Male			
Responder	3 (9%)	42 (63%)	36 (56%)
Odds ratio vs PBO+MTX [b.]		16.7 [4.6, 60.9]	12.1 [3.3, 44]
Female			
Responder	24 (14.5%)	186 (58%)	200 (62%)
Odds ratio vs PBO+MTX [b.]		8.36 [5.1, 13.5]	9.97 [6.0, 16.1]
Caucasian			
Responder	21 (12%)	209 (58%)	209 (60%)
Odds ratio vs PBO+MTX [b.]		10.6 [6.43, 17.6]	11.6 [7, 19.3]
Non-Caucasian			
Responder	6 (32%)	19 (66%)	27 (66%)
Odds ratio vs PBO+MTX [b.]		NP	NP
Disease Duration ≤ 3 years			
Responder	8 (14%)	68 (58%)	72 (57%)
Odds ratio vs PBO+MTX [b.]		8.26 [3.5, 19.1]	8.45 [3.68, 19.4]
Disease Duration > 3 years			
Responder	19 (14%)	160 (59%)	164 (63%)
Odds ratio vs PBO+MTX [b.]		9.7 [5.62, 16.72]	11 [6.32, 18.9]
Baseline Steroid Use - Yes			
Responder	18 (16%)	132 (56%)	149 (64%)
Odds ratio vs PBO+MTX [b.]		6.9 [3.9, 12.3]	9.45 [5.3, 16.7]
Baseline Steroid Use - No			
Responder	9 (11%)	96 (62%)	87 (57%)
Odds ratio vs PBO+MTX [b.]		14.48 [6.7, 31.23]	11.35 [5.2, 24.39]
Previous DMARDs > 0			
Responder	14 (11%)	156 (60%)	171 (64%)
Odds ratio vs PBO+MTX [b.]		12.5 [6.7, 22.8]	14.7 [0.8, 1.7]
Previous DMARDs 0			
Responder	13 (19%)	72 (57%)	65 (54%)
Odds ratio vs PBO+MTX [b.]		5.8 [2.8, 11.7]	5.2 [2.6, 10.6]
Previous Anti-TNF Use n =	7	11	16
Responder	2 (29%)	8 (73%)	13 (81%)
Odds ratio vs PBO+MTX [b.]		NP	NP
No Previous TNF Use n =	191	377	372
Responder	25 (13%)	220 (58%)	223 (60%)
Odds ratio vs PBO+MTX [b.]		9.45 [5.9, 15.1]	10.13 [6.3, 16.2]
Anti-CZP Antibody Positive n =	0	42	8
Responder		20 (48%)	4 (50%)
Odds ratio vs PBO+MTX [b.]		NP	NP
Anti-CZP Antibody Negative n =	193	346	380
Responder	26 (14%)	208 (60%)	232 (61%)
Odds ratio vs PBO+MTX [b.]		9.9 [6.2, 15.8]	10.3 [6.5, 16.4]

Revised from multiple sponsor Tables: 14.2.1:7 through Table 14.2.1:22, pages 1274 through 1326 of 8823

6.1.6 Other Endpoints – Study 027

Anti-CZP Antibody Status - Study 027

A patient was considered positive for anti-CZP antibody if the level was > 2.4 U/mL on at least one visit. In the CZP 200 mg group, patients with anti-CZP antibodies (n=42) had lower geometric mean CZP plasma concentrations at all visits from Week 4 to 52 compared with patients who tested negative (n=350). Due to the small number of antibody positive patients, it was difficult to reach any meaningful conclusions. The Safety Population showed 50 of 781 (6%) patients tested positive to anti-CZP antibodies at any time during Study 027. The incidence of antibody (among patients with antibody data) showed a small increase from Week 6 (0.1%) to a peak at Week 12 (3%). At Week 52, the incidence of anti-CZP antibody was at 4%.

Antibody detection was higher in the CZP 200 mg group (11%) than in the CZP 400 mg group (2%). The detection of anti-CZP antibodies can be hampered by the presence of CZP in the plasma, which may lead to false negative results and, therefore, to an underestimation of the incidence of the presence of antibody. See **Table 46** and **47**.

Table 46. Anti-CZP Antibody Status in Study 027

Anti-CZP Antibody Status in Study 027 at Week 24 (ITT Population)				
Week 24	CZP 200 mg + MTX N = 393		CZP 400 mg + MTX N = 390	
	Ab +	Ab -	Ab +	Ab -
n (%)	42 (11%)	346 (89%)	8 (2%)	380 (98%)
Responder	20 (48%)	208 (60%)	4(50%)	232 (61%)

Table 47. Incidence, Anti-CZP Antibody (+) Detection by Treatment Group – Study 027

Incidence of Anti-CZP Antibody-Positive Detection by Treatment Group- Study 027 (Safety Population)		
Patient's rate of Ab+ status [a.]	CZP 200 mg q2w + MTX N =392	CZP 400mg sc q2w + MTX N =389
Week 8 Ab+ rate (n)	1.3% (378)	0.8% (374)
Week 12 Ab+ rate (n)	4.9% (370)	1.1% (364)
Week 24 Ab+ rate (n)	2.8% (254)	1.1% (278)
Week 36 Ab+ rate (n)	5.1% (234)	0.4% (252)
Week 52 Ab+ rate (n)	6.4% (251)	1.1% (261)
Last Withdrawal Ab+ rate (n)	7.7% (391)	1.3% (384)
(a.) Antibody-positive (Ab+) status was defined as > 2.4 U/mL in at least one visit excluding follow-up sampling period. Revised from sponsor Table 11:21, page 143 of 8823 and Source Table 14.3.10:2, page 6630 of 8823.		

Neutralizing bioassay results showed that only a minority of the patients who tested positive for anti-CZP antibodies had neutralizing antibody activity. A total of 34% of patients (19 of 56; 15 from the 200 mg group and 4 from the 400 mg group) had neutralizing antibody activity.

ACR Response at Week 24 by Anti-CZP Antibody Status - Study 027

To determine whether the development of antibodies to CZP reduced efficacy, we examined ACR20 response rates in antibody-positive and –negative patients. As shown in **Table 48**, ACR20 response rates were somewhat lower in anti-CZP antibody-positive patients (48% and

50%) in the CZP 200 mg and 400 mg groups, respectively) than in the antibody-negative patients. These data suggest that development of antibodies attenuates the clinical response.

Table 48. Comparison of ACR20 Responder Rate by Antibody Status at Week 24 – Study 027

Comparison of ACR20 Responder Rate by Antibody Status at Week 24 - Study 027 (ITT)					
	PBO + MTX N = 199	CZP 200 mg sc q2w + MTX N = 395		CZP 400 mg q2w + MTX N = 390	
Week 24		Ab -	Ab +	Ab -	Ab +
n (%)		346 (88%)	42 (11%)	380 (97%)	8 (2%)
Responder	26 (14%)	208 (60%)	20 (48%)	232 (61%)	4 (50%)
Treatment by subgroup interaction [a.] p-value = 0.978.					
Threshold definitions: Antibody -positive, Ab+ > 2.4 U/mL; antibody negative, Ab- ≤ 2.4 U/mL.					
(a.) Wald p-values for the comparison of the treatment groups were calculated using logistic regression with factors for treatment, subgroup, region and subgroup by treatment interaction. The ACR20 response rate by antibody status was not reported for Week 52. Revised from sponsor Table 14.2.1:22, page 1324 of 8823 and Table 11:21, page 143 of 8823.					

6.1.7 Subpopulations – Study 027

The relevant subpopulations are discussed as subgroups in Study 027 and are presented in the sections of this review for the secondary efficacy endpoint results.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations – Study 027

The dose finding studies across the CZP RA development program were adequate and Study 027 supports CZP 200 mg q2w + MTX and CZP 400 mg q2w + MTX in patients with active RA. The co-primary efficacy results, as measured by the ACR20 response at 24 weeks and the inhibition of progression of structural damage as measured by the change from Baseline of mTSS including the erosion and joint space narrowing score at 52 weeks, are similar across the two dose regimens. Therefore, the proposed dosage and administration for adults with CZP 400 mg subcutaneously initially at Week 0, 2, and 4 followed by the maintenance dose of CZP 200 mg q2w (+ MTX) is acceptable. See the labeling recommendations in the APPENDICES, Section 9.2 of this review.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects – Study 027

Both dose regimens, CZP 200 mg q2w + MTX and CZP 400 mg q2w + MTX, achieved an ACR20 response at Weeks 12 and 24 and achieved inhibition of progression of structural progression as measured by mTSS, at Weeks 24 and 52. These outcomes in Study 027 support the primary efficacy outcome in Study 050 for the ACR20 response at Week 24 and the major secondary efficacy outcome inhibition of progression of structural damage as measured by mTSS at Week 24. There was no evidence for tolerance effects in Study 027 because the efficacy persisted through Week 52.

6.1.10 Additional Efficacy Issues/Analyses – Study 027

All efficacy analyses are included in the appropriate subsections of Section 6.0 Review of Efficacy.

6.1.11 Summary of Efficacy – Study 027

Study 027 employed the lyophilized formulation of CIMZIA® which is not intended for the commercial market. The results for the co-primary endpoints, the ACR20 response at week 24 and the inhibition of progression of structural damage as measured by the change from Baseline of the mTSS at Week 52, both showed statistically significant efficacy for CZP 200 mg q2w + MTX and CZP 400 mg q2w + MTX. There were 59% and 61% ACR20 response in CZP 200 mg and CZP 400 mg q2w + MTX treatment groups, compared to 14% in the PBO + MTX group ($p<0.001$). The ACR-50 and -70 responses supported the co-primary efficacy outcome with the ACR20.

The calculation of the pre-specified percent inhibition measured by mTSS mean change from Baseline to Week 24 demonstrated 87% and 83% inhibition of progression of structural damage in the CZP 200 mg and 400 mg sc q2w + MTX groups, respectively, and at Week 52, showed 85% and 92% inhibition of progression of structural damage in the same treatment groups, respectively. The difference between the two CZP treatment groups was not significant ($p>0.05$). These results showed inhibition of progression of structural damage with both CZP dose regimens at Week 24 and Week 52. This level of inhibition exceeds the 75% level of inhibition that has been used to distinguish highly effective agents that "inhibit" from less effective agents that are described as "slowing radiographic progression".

The two key secondary efficacy endpoints, major clinical response, defined as ACR70 response at any two time-points 24 weeks apart during the study and at all assessments in between, and the sustained response, defined as ACR20 responders at both Weeks 24 and 52, were both statistically significant compared to PBO + MTX. There were 196 patients (50%) and 197 patients (51%) in the CZP 200 mg and 400 mg q2w + MTX groups, respectively, compared to 23 patients (12%) in the PBO + MTX group, who achieved a sustained clinical response. The magnitude of the treatment effect between the two active doses was not significant at Week 52 or at Week 24. It is important to note that there was no evidence of tolerance. A larger proportion of patients in both CZP treatment groups achieved a major clinical response compared to PBO + MTX. Both of the key secondary efficacy endpoints were supported by pre-specified sensitivity analysis, therefore, supporting the co-primary efficacy outcomes.

In both CZP groups, significant improvements in physical function were shown by the HAQ-DI and supported by the Physical Component Summary (PCS) of the SF-36 compared to the PBO + MTX group.

Overall, CZP 200 mg and 400 mg q2w + MTX treatment groups showed a consistent effect for comparison of the ACR20 response across the subgroup analyses. Two trends were observed in Study 027 subgroup analyses:

1) Anti-CZP antibody negative patients tended to have higher ACR20 responses in both CZP 200 mg and 400 mg groups (60% and 61%, respectively) compared to anti-CZP antibody positive patients (48% and 50% response, respectively).

2) In Study 027 in both CZP 200 mg and 400 mg + MTX groups, RF positive patients tended to have higher ACR20 response rates, 62% and 62%, respectively, than did the RF negative patients, 48% and 55%, respectively. This trend has been observed with other TNF-inhibitors. Caution must be used in interpreting these data as the denominator was small in the RF negative patient population.

Overall, the treatment effect of CZP in Study 027 was consistent across the subgroups of age, gender, race, weight, BMI, disease duration, corticosteroid use, MTX dose, DAS28(ESR) class, CRP, ESR, region, nation or protocol version, in both active treatment groups as measured by the ACR20 at 24 Weeks and demonstrated support of the co-primary efficacy endpoint results favoring both CZP dose regimens compared to the PBO group. Study 027 demonstrated treatment effects with CZP 200 mg and 400 mg q2w + MTX that were comparable to those seen with other anti-TNF products.

6.2 Indication – Study 050

The proposed indication in patients with active RA in Study 050 is the same indication as reported in Study 027 under Section 6.1 of this review.

6.2.1 Methods – Study 050

The efficacy data contained in Section 6.2 of this review was generated from Study CDP870-050 (Study 050), a 24 week, randomized, placebo-controlled study, and was reviewed to assess the sponsor's efficacy submission. The analyses of the primary efficacy endpoint, the ACR20 response, and various secondary efficacy endpoints, as well as the analyses of the exploratory efficacy endpoints, were conducted for Study 050. All of the primary and key secondary efficacy endpoint analyses were confirmed by the FDA's statistical reviewer, Katherine Meaker, PhD. The primary efficacy endpoint, the ACR20 response, is discussed under Section 6.1.1 General Discussion of Endpoints. See Section 5.3 Discussion of Individual Studies for the protocol review of Study 050 and the schematic diagram of the study design.

6.2.2 Demographics –Study 050

The patient population was well balanced among the three treatment groups of patients with active RA. Overall, the majority of randomized patients were female, the average age was early 50s, and the majority of patients (98%) were Caucasian. See **Table 49**. Overall, the demographics were consistent with Study 027 and representative of the RA population.

Table 49. Patient Demographics – Study 050

Patient Demographics - Study 050 (ITT Population)				
	PBO + MTX N = 127	CZP 200 mg sc q2w + MTX N =246	CZp 400 mg sc q 2w + MTX N = 246	Overall N =619
Age (yrs.)				
Mean (SD)	52 (12)	52 (11)	52 (12)	52 (12)
Gender n(%)				
Male	20 (16%)	40 (16%)	54 (22%)	114 (18%)
Female	107 (84%)	206 (84%)	192 (78%)	505 (82%)
Race n (%)				
Caucasian	126 (99%)	239 (97%)	242 (98%)	607 (98%)
Weight				
Mean (SD)	72 (15)	73 (15)	73 (15)	73 (15)
BMI (kg/m^2)				
< 18.5 kg/m^2	2 (2%)	5 (2%)	4 (2%)	11 (2%)
18.5 to <30 kg/m^2	100 (58%)	185 (75%)	187 (76%)	472 (76%)
≥ 30 kg/m^2	25 (20%)	56 (23%)	55 (22%)	136 (22%)

Abbreviations: SD=standard deviation; yrs.=years; kg=kilogram; m=meter; MTX= methotrexate; PBO=placebo; BMI=Body Mass Index.
Revised from sponsor Table 11:2, page 81 of 6142.

In general, the Baseline RA disease characteristics in Study 050 were comparable across the 3 treatment groups as well as comparable to Study 027. In Study 050, the mean disease duration was 6 years, RF positive results were reported in 77% of enrolled patients, and the tender joint count and the swollen joint counts were 30 and 21, respectively.

Overall, the Baseline scores in the SF-36 component summaries, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), and the 8 domains, were comparable in Study 050. In summary, the HAQ-DI demonstrated a mean of 1.6 and the mean DAS28ESR was 6.8, demonstrating moderate to severe impairment in physical function and comparability to Study 027. See **Tables 50, 51** and **52.**

Table 50. Disease Characteristics – Study 050

Rheumatoid Arthritis History and Baseline Characteristics - Study 050				
History	PBO + MTX N = 127	CZP 200 mg sc q2w + MTX N =246	CZP 400 mg sc q2w + MTX N = 246	Overall N =619
Disease Duration (yrs.) [a]				
Mean (SD)	6 (4)	6 (4)	7 (4)	6 (4)
Disease Duration Class n(%) [a]				
≤ 3 years	41 (32%)	74 (30%)	73 (30%)	188 (30%)
> 3 years	86 (68%)	172 (70%)	173 (70%)	431 (70%)
Concomitant MTX Dose (mg/wk) [b]				
Mean (SD)	12 (3)	13 (4)	13 (4)	13 (4)
Concomitant MTX Dose Class (mg/wk) [b]				
< 10	1 (1%)	0	1 (0%)	2 (0%)
≥ 10 to < 25	124 (98%)	241 (98%	238 (97%)	603 (97%)
Extra articular Features (Any History) n (%)				
Nodules	21 (17%)	41 (17%)	39 (16%)	101 (16%)
Vasculitis	1 (1%)	2(1%)	7 (3%)	10 (2%)
Neuropathy	2 (2%)	6 (3%)	4 (2%)	12 (2%)
Other location/site	15 (12%)	36 (15%)	37 (15%)	88 (14%)
Extra articular Features n (%) [a]				
Nodules	20 (16%)	31 (13%)	31 (13%)	82 (13%)
Vasculitis	0	0	2 (1%)	2 (0%)
Neuropathy	1 (1%)	4 (2%)	5 (2%)	10 (2%)
Other location/site	12 (9%)	23 (9%)	26 (11%)	61 (10%)
# Pts. of Previous DMARDS				
Mean (SD)	1 (1)	1 (1)	1 (1)	1 (1)
Number of Previous DMARDS n (%)				
0	42 (33%)	91 (37%)	78 (32%)	211 (34%)
1	39 (31%)	71 (29%)	85 (35%)	195 (32%)
2	27 (21%)	42 (17%)	44 (18%)	113 (18%)
≥ 3	19 (15%)	42 (17%)	39 (16%)	100 (16%)
Baseline Corticosteroids Use n(%)				
Yes	76 (60%)	136 (55%)	152 (62%)	364 (59%)
Previous Anti-TNF Use n (%) [c]				
Yes	6 (5%)	9 (4%)	15 (6%)	30 (5%)

(a.) At Screening; (b.) There is discrepancy with the line Listing 16.2.4:5, pages 1365-1402. These data exclude 6 patients (#172/0002 from the PBO+MTX group; # 160/0002 from the CZP 200 mg + MTX group; # 104/0015, # 121/0009, # 132/0009, # 500/0003 and # 603/0016 from CZP 400 mg + MTX group) whose weekly MTX dose was incorrently transcribed as a daily dose.
(c.) Anti-TNF and other biological treatment are considered.

Table 51. Rheumatoid Arthritis Baseline Characteristics – Study 050

Rheumatoid Arthritis Baseline Characteristics - Study 050 (ITT Population)				
	PBO + MTX N = 127	CZP 200 mg sc q2w + MTX N = 246	CZP 400 mg sc q2w + MTX N = 246	Overall N =619
Tender/Painful Joint Count [a]				
Mean (SD)	30 (13)	30 (14)	30 (14)	30 (14)
Swollen Joint Count [b]				
Mean (SD)	22 (10)	20 (10)	21 (10)	21 (10)
Pts. Global Assessment of Arthritis (0-100mm VAS)				
Mean (SD)	60 (22)	62 (20)	61 (20)	61 (20)
Physician's Global Assessment of Arthritis Pain [c] (0-100 VAS)				
Mean (SD)	66 (15)	64 (15)	63 (14)	64 (15)
Patient's Assessment of Arthritis Pain [c] (0-100 mm VAS)				
Mean (SD)	60 (22)	62 (19)	60 (20)	61 (20)
HAQ Disability Index [d]				
Mean (SD)	2 (1)	2 (1)	2 (1)	2 (1)
Fatigue Assessment Scale				
Mean (SD)	7 (2)	7 (2)	6 (2)	N.A.
Duration of Morning Stiffness (hrs)				
Mean (SD)	3 (4)	3 (3)	3 (3)	3 (3)
DAS28 (ESR) [e]				
Mean (SD)	7 (1)	7 (1)	7 (1)	7 (1)
DAS28 (ESR) Class				
≥ 3.2 to ≤ 5.1	2 (2%)	5 (2%)	3 (1%)	10 (2%)
> 5.1	122 (98%)	241 (98%)	241 (99%)	604 (98%)
CRP Class				
Baseline ≤ 15 mg/L	59 (47%)	113 (46%)	129 (52%)	301 (49%)
Baseline > 15 mg/L	68 (53%)	133 (54%)	117 (48%)	318 (51%)
ESR Class				
Baseline < 30 mm / hour	16 (13%)	15 (6%)	26 (11%)	57 (9%)
Baseline ≥ 30 mm / hour	111 (87%)	231 (94%)	218 (89%)	560 (91%)
Rheumatoid Factor				
Negative (< 14 IU/mL)	27 (22%)	54 (23%)	58 (25%)	139 (23%)
Negative (≥ 14 IU/mL)	97 (78%)	186 (78%)	179 (76%)	462 (77%)
mTSS				
Mean (SD)	47 (59%)	40 (50%)	47 (56%)	N.A.
Joint Erosion Score				
Mean (SD)	23 (32)	19 (27)	22 (30)	N.A.
Joint Space Narrowing Score				
Mean (SD)	23 (28)	21 (24)	25 (28)	N.A.

(a.) Tender joint count ranges from 0-68; (b.) Swollen joint count ranges from 0-66; (c.) (0-100 mm Vas), lower disease activity, reuction in pain and in fatigue; (d.) HAQ-DI ranges from 0-3, lopwer scores indicate better physical function; (e.) DAS28(ESR)= 0.56 x sqrt (# tender/painful jts.) + 0.28 x sqrt (# swollen jts.) + 0.70 + ln(ESR) = 0.014 x (Pt. Global Assessment of Disease Activity - VAS.
Abbreviations: N.A.=not available; ESR=erythrocyte sedimentation rate; SD=standard deviation.
Revised from sponsor Table 14.1.4:4, pages 268 to 271.

Table 52. SF-36 Baseline Scores – Study 050

SF-36 Baseline Scores - Study 050 (ITT Population)			
SF-36 Component	PBO + MTX N = 127	CZP 200 mg sc q2w + MTX N =246	CZp 400 mg sc q2w + MTX N = 246
Physical Component Summary (PCS)			
Mean (SD)	31 (7)	31 (6)	31 (6)
Mental Component Summary (MCS)			
Mean (SD)	40 (11)	39 (11)	39 (11)

ITT= intent-to-treat population/ MTX-methotrexate.
Revised from sponsor Table 11:6, page 88 of 6142; Source Table 14.5.2:1 and Table 14.5.2:6).

PPD Skin Test at Screening – Study 050
A total of 44% of patients in Study 050 had no reaction to PPD skin tests at Screening. A majority of patients who did have reactions had indurations of 1 to 5 mm in diameter.

In Study 050, skin indurations of 1-5mm were considered negative and those of ≥ 6mm were considered positive. By current standards, negative would be 1-4mm and positive ≥5mm. Upon enrollment in Study 050, patients with a past history of vaccination with BCG were assumed to have positive PPD skin test results due to BCG. Ongoing studies were amended by the sponsor to reflect current guidelines such that a positive PPD would be assumed to reflect latent tuberculosis infection, regardless of whether or not the patient had previously received BCG.

Concurrent Medications for RA – Study 050
The proportion of patients taking concurrent medications at Baseline was similar across the 3 treatment groups. All the patients in each treatment group had at least 1 concurrent medication at Baseline since all the patients in Study 050 were receiving MTX, per the protocol. Among the patients taking anti-inflammatory medication for their RA, the next most common medications were diclofencac and methylprednisolone. **Tables 53** and **54** demonstrate the concomitant medications taken by ≥ 10% of patients in Study 050.

The most common prior RA medication was MTX, used by all patients, per protocol, followed by sulfasalazine used by similar proportions of patients in each treatment group.

Table 53. Concurrent Medications – Study 050

Concurrent Medications at Baseline Taken by ≥ 10% of Patients - Study 050 (ITT Population)				
Medication	PBO + MTX N =127	CZP 200 mg sc q2w + MTX N = 246	CZp 400 mg sc q2w + MTX N = 246	Overall N =619
# Pts. with ≥ 1 concurrent medication at Baseline	127	246	246	619
Methotrexate	127 (100%)	246 (100%)	246 (100%)	619 (100%)
Folic Acid	84 (66%)	155 (63%)	152 (62%)	391 (63%)
Diclofenac	37 (29%)	86 (35%)	85 (35%)	208 (34%)
Methylprednisolone	44 (35%)	64 (26%)	75 (31%)	183 (30%)
Prednisone	15 (12%)	37 (15%)	43 (18%)	95 (15%)
Nimesulide	19 (15%)	34 (14%)	41 (17%)	94 (15%)
Omeprazole	17 (13%)	39 (16%)	37 (15%)	93 (15%)
Meloxicam	21 (17%)	27 (11%)	33 (13%)	81 (13%)
Prednisone	16 (13%)	31 (13%)	31 (13%)	78 (13%)
Enalapril	9 (7%)	26 (111%)	19 (8%)	54 (9%)
Celecoxib	14 (11%)	21 (9%)	15 (6%)	50 (8%)

Revised from sponsor table 11:7, page 91 of 6142; Source Table 14.1.6:1

Table 54. Disease Modifying Anti-inflammatory Drugs – Study 050

Past DMARD Medication for RA - Study 050 (ITT Population)				
	PBO+MTX N = 127	CZP 200 mg sc q2w + MTX N = 246	CZP 400 mg sc q2w + MTX N = 246	Overall N =619
# Pts. with ≥ 1 concurrent medication	127	246	246	619
Methotrexate	127	246	246	619
Sulfasalazine	51 (40%)	93 (38%)	90 (37%)	234 (38%)
Chloroquine	27 (21%)	53 (22%)	63 (26%)	143 (23%)
Hydroxychloroquine	16 (13%)	36 (15%)	34 (14%)	86 (14%)
Sodium Aurothiomalate	18 914%)	30 (12%)	30 912%)	78 (13%)
Leflunomide	14 (11%)	25 (10%)	18 (7%)	57 (9%)
Revsied from sponsor Table 11:10, page 95 of 6142.				

TNF-Inhibitor Therapy – Study 050

The number of patients who used TNF inhibitor or other biologic therapy for RA was small (30 patients, 5%) in Study 050. See **Table 55.** This small number was the result of the exclusion criteria for patients who would have received any biological therapy for RA within 6 months prior to Baseline, except for etanercept and anakinra where 3 months prior to Baseline was acceptable.

Table 55. Past TNF Inhibitor and Other Biological Medications – Study 050

Anti-TNF Inhibitors or Other Biological Medications for RA - Study 050 (ITT Population)				
	PBO+MTX N = 127	CZP 200 mg sc q2w + MTX N = 246	CZP 400 mg sc q2w + MTX N = 246	Overall N =619
# Pts. with ≥ 1 past anti-TNF or other biological medication	6 (5%)	9 (4%)	15 (6%)	30 (5%)
Natalizumab	4 (3%)	6 (2%)	9 (4%)	19 (3%)
Infliximab	2 (2%)	3 (1%)	1 (0%)	6 (1%)
Etanercept	0	2 (1%)	2 (1%)	4 (1%)
Tocilizumab	0	2 (1%)	1 (0%)	3 (1%)
Interferon	0	0	2 (1%)	2 (0%)
Monoclonal antibodies [a.]	0	0	2 (1%)	2 (0%)
Rituximab	0	1 (0%)	0	1 (0%)
Adalimimab [b.]	0	1 (0%)	1 (0%)	2 (0%)
Anakinra [b.]	1 (1%)	1 (0%)	1 (0%)	3 (1%)

(a.) Anti-integrin therapy; (b.) Adalimumab and anakinra were reported in the line listing of Source Table 14.1.6:4, page 329 to336. Revised from sponsor Table 11:11, page 95 of 6142

Rescue Medication – Study 050

Rescue medication was used by 9%, 11% and 7% of the patients in the PBO + MTX, CZP 200 mg sc q2w + MTX, and CZP 400 mg sc q2w + MTX treatment groups, respectively. The use of rescue medication was similar across the study arms.

Measurement of Treatment Compliance – Study 050

The mean number of days between consecutive injections for the 2-week scheduled treatment intervals was similar among the 3 treatment groups with a range of 13.9 to 15.5 days. Study compliance, by study visit, relative to Baseline was almost identical between treatment groups at all time-points. For all treatment groups, the median was 14 days for all 2-week scheduled treatment intervals.

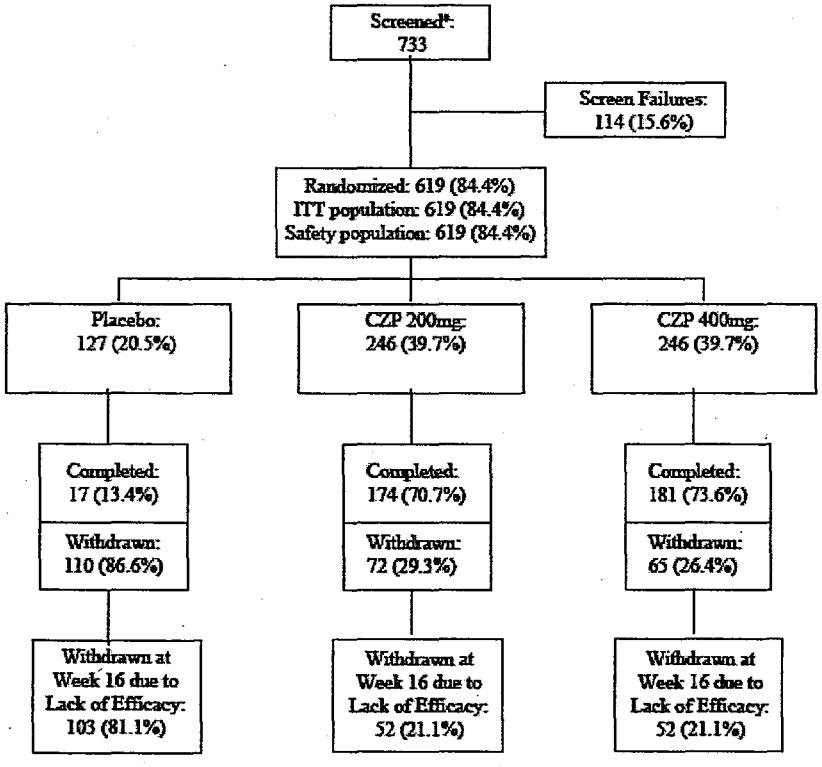
In summary, the overall Baseline characteristics across the 3 treatment groups in Study 050 were well balanced. The use of rescue medication was similar across the three treatment groups as was the compliance across the three treatment groups.

6.2.3 Patient Disposition – Study 050

A total of 733 patients were screened in Study 050, excluding those patients from the Lithuania site of Dr. Paksys, and 114 (16%) patients were screen failures. Therefore, there were 619 patients randomized into a ratio of 1:2:2. Of the 619 who were randomized and received the active biologic product, 372 (60%) completed the study. See **Figure 9** and **Table 56.** There were 207 patients (33%) who discontinued at Week 16 due to lack of efficacy and, overall, 247 (40%) of the patients who discontinued from Study 050. See **Table 57.**

The most common reason for withdrawal in the PBO + MTX group was lack of efficacy, being a non-responder at Week 12, confirmed at Week14 (pre-specified) and the subsequent mandatory discontinuation at Week 16. Patients from Study 050 were eligible to enter the open-label extension Study 051 if they withdrew at Week 16 or if they completed Study 050 and desired to continue treatment with CZP. Patients who entered Study 051 prior to completing all of the study visits were to have a follow-up visit 24 weeks after their CZP Study 050 Baseline visit.

Figure 9. Disposition of Patients – Study 050



(a.) Excluding 15 patients from Site 104 (Dr. Paksys) in Lithuania. Figure is sponsor Figure 10:1, page 77 of 6142.

Table 56. Patient Disposition – Study 050

Patient Disposition - Study 050 (ITT)				
	PBO + MTX N = 127	CZP 200 mg q2w + MTX N = 246	CZP 400 mg q 2w + MTX N = 246	Overall N = 619
All Patients				733
Screening Failures				114 (16%)
Randomized (ITT Population)	127	246	246	619 (100%)
Safety Population	125 (98%)	248 (100%)	246 (100%)	619 (100%)
PP (signs and symptoms)	125 (98%)	231 (94%)	238 (97%)	594 (96%)
Completed at Week 16	118 (93%)	228 (93%)	236 (96%)	582 (94%)
Discontinued at Week 16 due to Lack of Efficacy	103 (91%)	52 (21%)	52 (21%)	207 (33%)
Completed at Week 24	17 (13%)	174 (71%)	181 (74%)	372 (60%)
Total Discontinuations	110 (87%)	72 (29%)	65 (26%)	247 (40%)
Lack of Efficacy	107 (84%)	54 (22%)	53 (22%)	214 (35%)
Discontinued Due to AEs	2 (2%)	11 (5%)	6 (2%)	19 (3%)
Protocol Violations	1 (1%)	1 (0%)	2 (1%)	4 (1%)
Patient Decision, Consent w/dr.	0	5 (2%)	3 (1%)	8 (1%)
Lost to Follow-up	0	0	0	0
Other Reason	0	1 (0%)	1 (0%)	2 (0%)
# with ≥ 1 PPT Deviation(s)	2 (2%)	15 (6%)	9 (3%)	25 (4%)
Pts. with non-missing data for the primary efficacy endpoint [a.]	97%	93%	96%	95%

(a.) Patients with adequate data who completed or dropped out due to lack of efficacy. Therefore, the data is adequate to calculate the primary endpoint efficacy analysis for ACR20 responders at Week 24.
Percentages are based on ITT population. Abbreviations: Pop.=population; ITT=intent-to-treat; AEs= adverse events; PP=per protocol; PPT= per protocol total. Revised from sponsor Table 14.1.1 thru 5, pp 224-228 0f 6142.

Proportion of Patients Randomized by Region and Country - Study 050

This study was conducted in 76 centers in the following 13 countries: Bulgaria (3 centers), Croatia (1), Czech Republic (8), Estonia (1), Israel (8), Latvia (2), Lithuania (4), Poland (6), Russia (9), Serbia (4), Slovakia (4), Ukraine (10), and the United States (16). Due to questionable data and a serious breach of Good Clinical Practice (GCP) at one site (Site # 104) in Lithuania, the data from that site was excluded from the analyses performed. See **Table 57.**

Table 57. Proportion of Patients Randomized by Region and Country – Study 050

Proportion of Patients Randomized by Region and Country - Study 050 (ITT Pop.)				
Region / Country	PBO + MTX N = 127	CZP 200 mg q2w + MTX N = 246	CZP 400 mg q2w + MTX N = 246	Overall N = 619
Russian, Baltic States and Scandinavia	53 (42%)	98 (40%)	101 (41%)	252 (41%)
Estonia	2 (2%)	3 (2%)	2 (1%)	7 (1%)
Lativa	3 (2%)	6 (2%)	6 (2%)	15 (2%)
Lithuania	10 (8%)	16 (7%)	19 (8%)	45 (7%)
Russian	23 (18%)	45 (18%)	46 (19%)	114 (18%)
Ukraine	15 (12%)	28 (11%)	28 (11%)	71 (12%)
Eastern Europe	61 (48%)	118 (48%)	123 (50)	302 (49%)
Bulgaria	3 (2%)	6 (2%)	9 (4%)	18 (3%)
Croatia	2 (2%)	4 (2%)	4 (2%)	10 (2%)
Czech Republic	20 (16%)	38 (15%)	40 (16%)	98 (16%)
Poland	18 (14%)	38 (15%)	36 (15%)	92 (15%)
Serbia	11 (9%)	20 (8%)	21 (9%)	52 (8%)
Slovakia	7 (6%)	12 (5%)	13 (5%)	32 (5%)
Rest of the World	13 (10%)	10 (12%)	22 (9%)	65 (11%)
Israel	4 (3%)	9 (4%)	5 (2%)	18 (3%)
United States	9 (7%)	21 (9%)	17 (7%)	47 (8%)

Revised from sponsor Table 14.1.1:6, pages 229 through 233 of 6142

6.2.4 Analysis of Primary Endpoint(s) – Study 050

The pivotal Phase 3 Study 050 was a 24 week, randomized, placebo-controlled trial designed to evaluate CZP in patients with active RA who have an incomplete response to MTX. This was the only study in this BLA submission that employed the intended to be marketed liquid formulation of CZP. The primary efficacy endpoint was the ACR20 response rate at 24 weeks. Study 050 also assessed the key secondary efficacy endpoints: inhibition of progression of structural damage as measured by mTSS at week 24 and the HAQ-DI to assess physical function.

Study 050 demonstrated statistically significant and clinically meaningful efficacy as measured by the ACR20 response at Week 24 with 57% and 58% of patients in the CZP 200 mg + MTX and CZP 400 mg + MTX group, respectively, compared to 9% of patients in the PBO + MTX treatment group ($p<0.001$). The odds ratio measured the odds of a response in one group compared to another, i.e., an odds ratio of greater than 1.0 expresses the magnitude by which the odds of improvement in the first group exceeded the odds of improving in the second; an odds ratio of 1 indicating no difference. See **Table 58.** The small differences between the active treatment groups were not statistically significant or clinically meaningful.

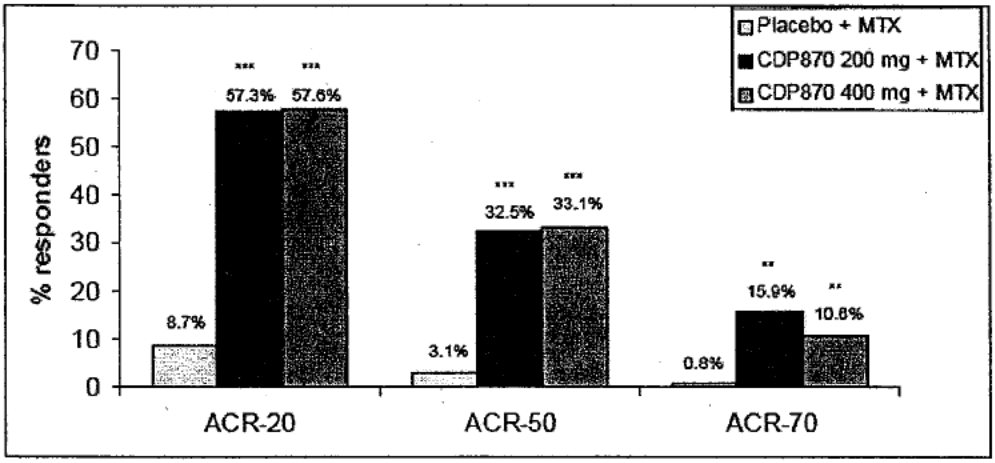
A larger percentage of patients in the CZP 200 mg + MTX and CZP 400 mg + MTX treatment groups achieved the ACR20, ACR50 and ACR70 response at Week 24 than did patients in the PBO + MTX treatment group. See **Figure 10.** The odds ratios versus the control were statistically significantly greater than 1 in both CZP treatment groups for each of these endpoints ($p<0.001$ for the ACR20 and ACR50 and $p\leq 0.01$ for the ACR70). The PBO + MTX treatment group demonstrated low ACR response rates (9%) at Week 24. As pre-specified in the protocol, non-responders in Study 050 at Weeks 12 and 14 were designated as treatment failures. There were 103 (81%) of 127 patients in the PBO + MTX group who discontinued due to lack of efficacy at Week 16. Therefore, only the remaining 19% of patients had an opportunity to achieve an ACR response at the later visits.

Table 58. ACR-20, -50 and -70 Responses – Study 050

ACR Response - Study 050 (ITT Population) - Study 050			
	PBO + MTX N = 127	CZP 200 mg sc q2w + MTX N = 246	CZP 400 mg sc q2w + MTX N = 246
ACR-20 at Week 24			
n	127	246	245
Responder	11 (9%)	141 (57%)	141 (58%)
Odds ratio vs PBO + MTX [a.]		14	14
97.5% CI for odds ratio		[7, 31]	[7, 31]
p-value [c.]		<0.001	<0.001
Odds ratio vs CZP 200 mg q2w + MTX [b.]			1
95% CI for odds ratio			[1, 1]
p-value [c.]			1
ACR-50 at Week 24			
Responder	4 (3%)	80 (33%)	81 (33%)
Odds ratio vs PBO + MTX [a.]		17	12
95% CI for odds ratio		[3, 118]	[2, 80]
p-value [c.]		0.004	0.011
Odds ratio vs CZP 200 mg + MTX [b.]			1
95% CI for odds ratio			[1, 2]
p-value [c.]			0.9
Treatment by Region Interaction [d.] p-value = 0.50			
ACR-70 at Week 24			
Responder	1 (0%)	39 (16%)	26 (11%)
Odds ratio vs PBO + MTX [a.]		24	15
95% CI for odds ratio		[3, 176]	[2, 115]
p-value [c.]		0.002	0.008
Odds ratio vs CZP 200 mg + MTX [b.]			0.6
95% CI for odds ratio			[0, 1]
p-value [c.]			0.113
Treatment by Region Interaction [d.] p-value = 0.14			

(a.) Odds ratio: CZP/PBO calculated using the logistic regression with factors for tx, and region.
(b.) Odds ratio: CZP 400 mg/ CZP 200 mg calculated using logistic regression with factors for treatment and region.
(c.) Wald p-value for the comparison of treatment groups was calculated using logistic regression with factors for treatment and region.
(d.) Wald p-value was calculated using logistic regression with treatment and region and treatment by region interaction as factors. Abbreviations: tx = treatment. Revised from sponsor Table 14.2.4.3, page 787 of 6142.

Figure 10. ACR 20/50/70 Response – Study 050



Notes: *** indicates p <0.001; ** indicates p ≤0.01; P-values for comparison of treatment groups were based on odds ratio (versus PBO + MTX) rather than percent responders. CDP870 is CZP.
Source: Table 14.2.1:1, Table 14.2.4:1 and Table 14.2.4:3

Sensitivity Analyses – Study 050

The pre-specified sensitivity analyses at Week 24 supported the primary efficacy analyses in Study 050. These pre-specified analyses were based on the ITT population and included specific imputation rules technique, LOCF approach and multiple imputation analysis. The first sensitivity analysis used the following algorithm: patients withdrawing before Week 16, regardless of their final outcomes, were considered as ACR20 non-responders at Week 24. Patients who dropped out at or after Week 16 but before Week 24, and were ACR20 non-responders at the time of withdrawal, were considered ACR20 non-responders at Week 24. The remaining patients assigned to treatment with CZP were considered as ACR20 responders at Week 24, if the withdrawals occurred at or after Week 16 but before Week 24 and if they were ACR20 responders at the time of withdrawal and also at the last visit prior to the withdrawal. The remaining CZP patients who dropped out of the study at or after Week 16 but before Week 24 were considered ACR20 non-responders at Weeek24 if they did not satisfy the criteria described above. See **Table 59.**

Table 59. ACR20 Responder Rates - Sensitivity Analyses - Study 050

ACR-20 Responder Rate at Week 24 - Sensitivty Analyses - Study 050			
	PBO + MTX N = 127	CZP 200mg sc q2w + MTX N = 246	CZP 400 mg sc q2w + MTX N = 246
Specific Imputation Rules - ITT Population			
Responder	16 (13%)	143 (58%)	147 (60%)
Odds ratio vs PBO+MTX [a.]		9.63	10.33
97.5% CI for odds ratio		[5, 18.7]	[5, 20]
p-value [c.]		<0.001	<0.001
Odds ratio vs CZP 200mg +MTX [b.]			1.07
95% CI for odds ratio			[0.74, 1.54]
p-value [c.]			
Last Observation Carried Forward (LOCF) ITT Population			
Responder	18 (14%)	164 (67%)	175 (71%)
Odds ratio vs PBO+MTX [a.]		12	15
97.5% CI for odds ratio		[6, 23]	[7, 28]
p-value [c.]		< 0.001	<0.001
Odds ratio vs CZP 200 mg+MTX [b.]			1
95% CI for odds ratio			[1, 2]
p-value [c.]			0.3
Multiple Imputation - ITT Population			
Responder	21 (17%)	176 (72%)	184 (75%)
Odds ratio vs PBO+MTX [a.]		8	9
97.5% CI for odds ratio		[5, 15]	[5, 16]
p-value [c.]		<0.001	<0.001
Odds ratio vs CZP 200 mg+MTX [b.]			1
95% CI for odds ratio			[1, 2]
p-value [c.]			0.7

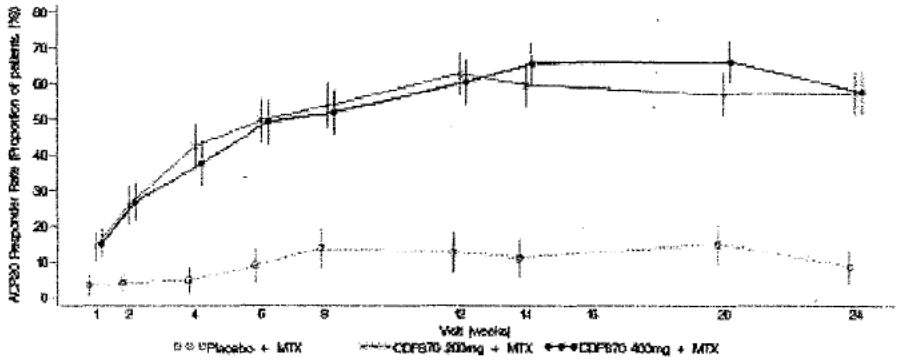
(a) Odds ratio: CDP870/Placebo calculated using logistic regression with factors for treatment and region.
(b) Odds ratio: CDP870 400mg/CDP870 200mg calculated using logistic regression with factors for treatment and region.
(c) Wald p-values for the comparison of the treatment groups have been calculated using logistic regression with factors for treatment and region.
Revised from sponsor Table 14.2.1:3, 4 and 5, page 6943 through 695 of 6142

6.2.5 Analysis of Secondary Endpoint(s) – Study 050

ACR20/50/70 Response over Time – Study 050

The ACR20 responder rates in the CZP treatment groups demonstrated a separation from PBO+MTX as early as Week 1, achieved a peak at Week 12 to 14, and were then maintained through to the end of the study at Week 24. The odds ratios versus control were statistically significantly greater than 1.0 in both CZP treatment groups ($p<0.001$ at Weeks 2 through 24; Week 1, $p=0.003$ for CZP 200 mg + MTX and $p=0.002$ for CZP 400 mg + MTX). See **Figure 11.** Overall, approximately 60% of patients responded by Week 12 in both CZP treatment groups and responder rates were maintained through Week 24. The ACR50 and ACR70 response rates showed a similar time course with the exception that the ACR70 responses in the active treatment arms did not begin to separate from the PBO + MTX group until Week 4.

Figure 11. ACR20 Responder Rate by Visit – Study 050



Note: The number of patients in each treatment group can slightly change across scheduled visits.
Note: The error bars denote 95% confidence intervals. CDP870 is CZP
Source: Figure 14.2.5.88

Change from Baseline in Individual ACR Components – Study 050

The ACR response criteria are based on seven components. We examined the individual components to determine whether the positive results on the overall ACR response were attributable to an effect of CZP on a few components or if the effects were more general. As shown in **Table 60**, all components of the ACR response showed improvement from Baseline in CZP treated patients.

Table 60. Percentage Change in the ACR Components and Duration of Morning Stiffness at Week 24

Percentage Change from Baseline in ACR Components at Week 24			
LOCF (ITT Population) -Study 050			
Parameter	PBO+MTX N = 127	CZP 200 mg sc q2w + MTX N = 246	CZP 400 mg sc q2w + MTX N = 246
Tender Joint Count			
Baseline (SD)	31 (13)	30 (14)	30 (14)
Week 12, Median	-5	-54	-61
Week 24, Median	-33	-85	-84
Swollen Joint Count			
Baseline (SD)	22 (10)	20 (10)	21 (10)
Week 12, Median	-8	-67	-63
Week 24, Median	-13	-73	-75
Patient's Assessment of Pain - VAS			
Baseline (SD)	60 (22)	62 (19)	61 (20)
Week 12, Median	-4	-31	-33
Week 24, Median	-4	-39	-41
Patient's Global Assessment of Disease Activity			
Baseline (SD)	60 (22)	62 (20)	61 (20)
Week 12, Median	-5	-33	-33
Week 24, Median	-4	-38	-42
Physician's Global Assessment of Disease Activity			
Baseline (SD)	66 (15)	64 (15)	63 (14)
Week 12, Median	-7	-48	-43
Week 24, Median	-7	-56	-54
Health Assessment of Quality - Disability Index			
Baseline (SD)	2 (1)	2 (1)	2 (1)
Week 12, Median	-7	-23	-24
Week 24, Median	-6	-29	-27
Duration of Morning Stiffness			
Baseline (SD)	3 (4)	3 (3)	3 (3)
Week 12, Median	-23	-75	-67
Week 24, Median	-25	-75	-75
C-Reactive Protein			
Baseline, Median	17	18	118
Week 12, Median	13	5	4
Week 24, Median	13	5.5	3.9
Revised from Table 14.2.5:13, page 902 of 6142; Table 14.2.5:19, page 944 of 6142; Table 14.2.5:25, page 989 of 6142; Table 14.2.5:31, page 1041 of 6142; Table14.2.5:37, page 1093 of 6142; Table 14.2.5:43, page 1137 of 6142; 14.2.5:58,page 1246 of 6142;			

Duration of Morning Stiffness - Study 050

The duration of morning stiffness (hours) was defined as the time elapsed between the time of usual awakening and the time the patient was limber as he/she would be during a day involving typical daily activities. This secondary endpoint was among many other secondary endpoints in Study 050. Both CZP treatment groups demonstrated a statistically significantly greater reduction in morning stiffness at each time point in the change from Baseline in the duration of morning stiffness compared to the PBO + MTX group ($p<0.001$). See **Table 61.** At Week 24, the median change from Baseline in the duration of morning stiffness was -1.3, -1.5 and -0.50 hours in the CZP 200 mg, CZP 400 mg and PBO + MTX treatment groups. In summary, this

improvement in the duration of morning stiffness is consistent with the results for the ACR20, 50 and 70 responses.

Table 61. Change from Baseline in Duration of Morning Stiffness – Study 050

Change from Baseline in Duration of Morning Stiffness (hours) - Study 050			
By Visit (LOCF) ITT Population			
Visit	PBO+MTX N=127	CZP 200 mg sc q2w + MTX N=246	CZP 400 mg sc q2w + MTX N=246
Baseline (SD)	3.3 (4)	2.6 (3)	2.6 (3)
Week 1, Mean (SD)	-0.1 (3)	-0.7 (2)	-0.6 (2)
Median	0	-0.50	-0.25
Week 12, Mean (SD)	-0.6 (3)	-1.5 (3)	-1.7 (2)
Median	-0.25	-1	-1
Week 24, Mean (SD)	-0.7 (3)	-1.6 (3)	-1.9 (3)
Median	-0.50	-1.3	-1.5

Abbreviations: LOCF=last observation carried forward; ITT-intent-to-treat; SD=standard deviation;
Revised from sponsor table 14.2.5:46, pages 1160-1164 of 6142

Key Secondary Efficacy endpoint
Inhibition of Progression of Structural Damage (mTSS) - Study 050
The key secondary efficacy endpoint, the inhibition of progression of structural damage, was assessed by the change from Baseline in the mTSS at Week 24 and was statistically significantly decreased in the CZP 200 mg + MTX ($p=0.003$) and in the CZP 400 mg + MTX ($p<0.001$) groups compared to PBO + MTX group. The reported difference between the two CZP doses was not significant ($p=0.087$). See **Table 62.**

For purposes of imputation, the mTSS score at Week 24 for the early withdrawal patients was estimated by linear extrapolation of the scores from the radiographs taken at the early Withdrawal visit. The radiographic claim in Study 050 (and 027) was based on the difference in radiographic scores in films taken at 6 months. For all responder analyses, it was pre-specified that patients who withdrew for nay reason or sued rescue medication were considered as non-responders from that time-point onwards, unless stated otherwise. The method of analysis involved ranking these data and then analyzing those ranks using ANCOVA.

For all responder analyses, patients who withdrew for any reason or used rescue medication were considered as non-responders from that time-point onwards, unless stated otherwise. As pre-specified, any missing data during the study prior to study completion/ withdrawal or use of rescue medication remained as missing at that time-point unless stated otherwise (e.g., LOCF).

The pre-specified sensitivity analyses (linear extrapolation and LOCF – ITT) demonstrated supportive results for the change from Baseline in mTSS scores. See **Table 64.** As modified in the protocol, the analysis of the major secondary efficacy endpoint, mTSS change from Baseline to Week 24, patients who withdrew before Week 24 and had radiographs taken at their early Withdrawal visit were included in this analysis. The overall method of analysis involved ranking the data and then analyzing those ranks using ANCOVA.

In order to gauge the magnitude of the effect of CZP, we examined the percent inhibition of mTSS using the mean change from Baseline in mTSS for the CZP treatment groups compared to the PBO + MTX groups. This analysis demonstrated that the percent inhibition achieved was 81% and 134% in the CZP 200 mg and 400 mg + MTX groups, respectively. This level of inhibition exceeds the 75% level of inhibition that has been used to distinguish highly effective agents that "inhibit" from less effective agents that are described as "slowing radiographic progression".

Table 62. Change from Baseline in mTSS, Erosion and Joint Space Narrowing, Week 24 (050)

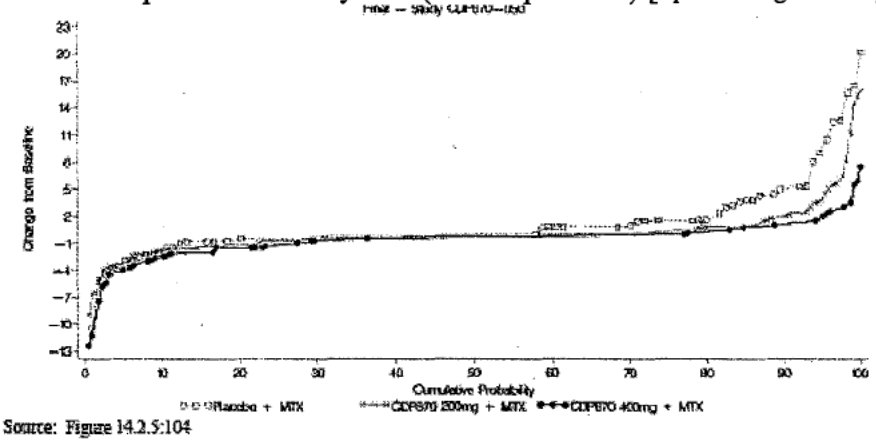
Change from Baseline in mTSS, Erosion and Joint Space Narrowing at Week 24 (ITT Population) - Study 050			
	PBO + MTX N = 127	CZP 200 mg sc q2w + MTX N = 246	CZP 400 mg sc q2w + MTX N = 246
mTSS			
Baseline			
N [e.]	125	241	240
Mean (SD)	47 (59)	40 (50)	47 (56)
Change from Baseline at Week 24			
N [f.]	112	214	222
Mean (SD)	1 (4)	0 (3)	-0.4 (2)
Difference [a.] vs PBO+MTX [b.]		-0.3	-0.7
95% CI for Difference		[-0.8, 0]	[-1, 0]
p-value		0.003	<0.001
% Inhibition vs PBO+ MTX [d.]		81	134
Erosion Score			
Baseline [N [e.]]			
Mean (SD)	23 (32)	19 (27)	22 (30)
Change from Baseline at Week 24 [N [f.]]			
Mean (SD)	0.7 (3)	0.1 (2)	-0.3 (2)
Difference [a.] vs PBO+MTX [b.]		0	-0.5
95 % CI for Difference		[-0.5, 0]	[-0.7, 0]
p-value		0.005	<0.001
Joint Space Narrowing Score			
Baseline [N [e.]]			
Mean (SD)	25 (28)	21 (24)	25 (28)
Change from Baseline at Week 24 [N [f.]]			
Mean (SD)	0.5 (2)	0.1 (1)	-0.1 (10)
Difference (a.) vs PBO+MTX [b.]		0	0
95% CI for difference		[0, 0]	[0, 0]
p-value		0.004	0.004

(a.) The differences are presented as CZP200 mg/CZP400 mg +MTX minus PBO+MTX.
(b.) Hodges-Lehman point estimate of shift and CI.
(c.) ANCOVA on the ranks with region and treatment as factors and rank Baseline as a covariate.
(d.) % Inhibition = 1 (change from Baseline in mTSS in CZP group/change from Baseline in mTSS in PBO+MTX treatment)*100.
(e.) N is the same number of patients as reported for mTSS.
(f.) N is the same number of patients as reported for mTSS.
Revised from sponsor Table 11:14, page 110 to 111 of 8142.

Cumulative probability plots are useful for displaying the distribution of values for radiographic progression and comparing results between study arms. A cumulative distribution plot for Study 050 is shown in **Figure 11.** From the cumulative probability plot, the proportion of patients exhibiting a value less than or equal to the values of change in the mTSS from Baseline on the y-axis can be read on the x-axis. The cumulative probability plot demonstrates that for any positive value of radiographic progression, the likelihood of progression was greater for the PBO + MTX group than for the both the CZP groups.

The cumulative probability plot suggests that the CZP 400 mg dose regimen was more effective for inhibiting radiographic progression than the CZP 200 mg dose regimen. Nonetheless, both CZP doses were associated with less radiographic progression than PBO + MTX.

Figure 11. Cumulative Probability Plot of the Change from Baseline in mTSS at Week 24 – Linear Extrapolation – Study 050 (ITT Population) [Sponsor Figure 11:8) page 112 of 6142.]



Source: Figure 14.2.5:104

Changes from Baseline in the Erosion Score and Joint Space Narrowing Score – Study 050
The changes from Baseline in the erosion score at Week 24 were statistically significantly decreased in both CZP + MTX treatment groups as compared to PBO + MTX ($p \leq 0.01$). The changes from Baseline at Week 24 in joint space narrowing scores were statistically significantly decreased in both CZP + MTX treatment groups compared to PBO + MTX ($p=0.004$). See **Table 63.**

In summary, the results of statistically significant inhibition of the progression of structural damage, measured by the mTSS, with both CZP dose regimens was demonstrated at Week 24 in Study 050. This outcome supports the co-primary efficacy endpoint inhibition of progression of structural damage in Study 027 at Week 52, as well as at Week 24. In summary, both Study 050 and 027 support the proposed claim of radiographic response for CZP in patients with active RA.

Table 64. Sensitivity Analyses for mTSS – Study 050

Comparison of the Change from Baseline in mTSS at Week 24 - Linear Extrpolation - ITT - Study 050			
Treatment	PBO + MTX N = 127	CZP 200 mg sc q2w + MTX N = 246	CZP 400 mg sc q2w + MTX N = 246
n	112	214	222
Mean (SD)	1.2 (4.1)	0.2 (2.7)	-0.4 (2.1)
Median (Q1, Q3)	0 (0, 1.5)	0 (-0.5, 0.5)	0 (-1.0, 0)
Diff (a.) vs PBO+MTX [(c.)]		-0.3	-0.7
95% CI for Diff [(c.)]		[-0.8, 0]	[-1, 0]
p-value [(d.)]		0.003	<0.001
Diff (a.) vs CZP 200mg+MTX [(c.)]			0
95% CI for Diff [(c.)]			[-0.5, 0]
p-value [(d.)]			0.087
Treatment by Baseline Interaction [(e.)] p-value = 0.723			
Treatment by Region Interaction [(f.)] p-value = 0.663			
Comparison of the Change from Baseline in mTSS at Week 24 - LOCF - ITT - Study 050			
n	112	214	222
Mean (SD)	0.9 (2.9)	0.2 (2.3)	-0.4 (2.0)
Median (Q1, Q3)	0 (0, 1)	0 (-0.5, 0.5)	0 (-1.0, 0)
Diff (a.) vs PBO+MTX [(c.)]		-0.1	-0.5
95% CI for Diff [(c.)]		[-0.5, 0]	[-1.0, 0]
p-value [(d.)]		0.004	<0.001
Diff (a.) vs CZP 200mg+MTX [(c.)]			0
95% CI for Diff [(c.)]			[-0.5, 0]
p-value [(d.)]			0.095
Comparison of the Ratio to Baseline in mTSS at Week 24 -Observed Data - Log Transformed Data ITT			
n	14	145	156
Adj. Geometric mean	1.12	1.03	0.99
Ratio [(b.)] vs PBO+MTX [(a.)]			
Adj. Geometric Mean [95% CI]		0.91 [0.8, 1.0]	0.88 [0.8, 0.97]
p-value		0.065	0.008
Percent Reduction [95% CI] [(c.)]		8.6 [-0.6, 16.8]	12 [3.3, 20]
Ratio [(b.)] vs CZP 200mg+MTX [(a.)]			
Adj. Geometric Mean [95% CI]			0.96 [0.93, 1]
p-value			0.053
Percent Reduction [95% CI] [(c.)]			3.8 [-0.0, 7.5]

Revised from Sponsor Tables 14.2.2:1, page 771; Table 14.2.2:2, page 773; Table 14.2.2:3, page 775 of 6142
For the Comparison of Change from Baseline in mTSS at Week 24 –Linear Extrapolation
(a) The differences presented are 'CDP870 200mg/400mg + MTX minus PBO + MTX'.
(b) The difference presented is 'CDP870 400mg + MTX minus CDP870 200mg + MTX'.
(c) Hodges-Lehmann point estimate of shift and confidence interval (Proc StatXact).
(d) ANCOVA on the ranks with region, treatment as factors and rank baseline as a covariate.

For the Comparison of Change from Baseline in mTSS at Wk 24 – LOCF:
(a) The differences presented are 'CDP870 200mg/400mg + MTX minus PBO + MTX'.
(b) The difference presented is 'CDP870 400mg + MTX minus CDP870 200mg + MTX'.
(c) Hodges-Lehmann point estimate of shift and confidence interval (Proc StatXact).
(d) ANCOVA on the ranks with region, treatment as factors and rank baseline as a covariate.

For the Comparison of the Ratio to Baseline in mTSS
(a) ANCOVA on log transformed data with region and treatment as factors and baseline as a covariate.
(b) The ratios presented are 'CDP870 200mg/400mg + MTX over PBO + MTX'.
(c) Percent Reduction = 100 x [1 - ratio 'CDP870 200mg/400mg + MTX over PBO + MTX'].
(d) The ratio presented is 'CDP870 400mg + MTX over CDP870 200mg + MTX'.

(e) Percent Reduction = 100 x [1 - ratio 'CDP870 400mg + MTX over CDP870 200mg + MTX'].

Table 65 summarizes the missing and non-missing data from analysis of change from Baseline in mTSS at 24 Weeks (ITT population). These data clarify why the (n) in the different analyses do not represent the total ITT population. There were very few patients in the ITT population who had no x-ray data at all.

Two additional sensitivity analyses for mTSS at Week 24 (Study 050) were the following: 1) Change from baseline still missing after linear extrapolation at a specific time-point was imputed using the median of all valid observed changes from baseline at that time-point and 2) Change from baseline imputed for the post-baseline time-point, separately within treatment groups. See **Table 66.**

Table 65. Summary of Missing Data and Non-Missing Data from Analysis of Change from Baseline in mTSS at Week 24, Study 050 (ITT Population)

Summary of Missing Data and Non-Missing Data from Analysis of Change from Baseline in mTSS at Week 24, Study 050 (ITT Population)			
Treatment	PBO + MTX N=127	Czp 200 mg + MTX N=246	CZP 400 mg + MTX N=246
Pts. with observed data	16	172	178
Pts. with B/L and at least one post-B/L	112	214	222
Pts. without extrapolation	13	27	18
Pts. with no usable x-ray data	2	5	6
Pts. with missing B/L	1	0	1

Revised from Sponsor Table 17, (Information Request response July 18, 2008)

Table 66. Additional Sensitivity Analyses (mTSS) at Week 24 (ITT Population, Study 050)

Comparison of the Change from Baseline in the mTSS at Week 24 - Linear Extrapolation and Median Imputation of Change from Baseline by Baseline Quartile, Study 050 (ITT)			
Treatment	PBO + MTX N=127	CZP 200 mg + MTX N=246	CZP 400 mg + MTX N=246
n	125	241	240
Mean (SD)	1.1 (3.9)	0.2 (2.5)	-0.4 (2.0)
Median	0.0 (-11, 20)	0.0 (-9, 16)	0.0 (-13, 8)
Difference [a.] vs PBO+MTX [c.]		0	-0.5
95% CI for Difference [c.]		[-0.5, 0.0]	[-0.8, 0.0]
p-value [d.]		0.003	<0.001
Difference [b.] vs CZP 200 mg+MTX [c.]			0
95% CI for Difference [c.]			[0.0, 0.0]
p-value [d.]			0.089
Comparison of the Change from Baseline in the mTSS at Week 24 - Linear Extrapolation and Median Imputation of Change from Baseline by Baseline Quartile and Treatment Group, (050, ITT)			
n	125	241	240
Mean (SD)	1.2 (3.9)	0.2 (2.5)	-0.4 (2.0)
Median	0 (-11, 20)	0 (-9, 16)	0 (-13, 8)
Difference [a.] vs PBO+MTX [c.]		-0.5	-0.7
95% CI for Difference [c.]		[-0.8, 0.0]	[-1.0, -0.3]
p-value [d.]		<0.001	<0.001
Difference [b.] vs CZP 200 mg+MTX [c.]			0
95% CI for Difference [c.]			[0.0, 0.0]
p-value [d.]			0.126

a) The differences presented are 'CDP870 200mg/400mg + MTX minus PBO + MTX'.
(b) The difference presented is 'CDP870 400mg + MTX minus CDP870 200mg + MTX'.
(c) Hodges-Lehmann point estimate of shift and confidence interval (Proc StatXact).
(d) ANCOVA on the ranks with region, treatment as factors and rank baseline as a covariate.

Overall, the results demonstrate statistically significant inhibition of the progression of structural damage, measured by mTSS with both CZP dose regimens at Week 24 (key secondary endpoint). These outcomes were supported by the co-primary efficacy endpoint inhibition of progression of structural damage in Study 027 at 52 weeks and by the sensitivity analyses (050 and 027). In summary, Study 050 supports the proposed radiographic claim for CZP in RA.

Health Assessment Questionnaire- Disability Index (HAQ-DI) – Study 050
Physical Function

The Health Assessment Questionnaire-Disability Index (HAQ-DI) is a well accepted measure of physical function in clinical trials of RA. Studies in RA patients have demonstrated that changes exceeding 0.22 units, on a scale of 0 – 3, are clinically meaningful. The HAQ-DI is a continuous endpoint pre-specified to be analyzed using the mean change from Baseline at Week 24 using an analysis of covariance (ANCOVA) model with region and treatment group as factors and Baseline value as a covariate. Missing values because of a patient withdrawal or data exclusion after the use of rescue medication were imputed by carrying forward the last efficacy measurement (LOCF imputation). Pending - statistics reviewer to complete a non-responder imputation for the HAQ-DI. See Statistic Review by Kate Meaker, PhD.

As shown in **Table 67**, patients in both CZP treatment groups demonstrated statistically significant and clinically meaningful improvement in physical function over PBO + MTX ($p<0.001$) from Week 1 to Week 24.

Table 67. Health Assessment Questionnaire – Disability Index: Study 050

Comparison of Change from Baseline in HAQ-DI - Study 050 Week 24 - LOCF (ITT Population)			
	PBO + MTX	CZP 200 mg sc q2w + MTX	CZP 400 mg sc q2w + MTX
Week 24	N = 127	N = 246	N = 246
Adj. Mean (SE) [a.]	-0.1 (0)	-0.5 (0)	-0.5 (0)
Difference [b.] vs PBO+MTX [a.]			
Adj. Mean [95% CI]		-0.4 [-0.5, -0.3]	-0.4 [-0.5, -0.3]
P-value		<0.001	<0.001
(a.) ANCOVA with region and treatment as factors and Baseline as covariate.			
(b.) The differences presented are CZP 200mg/400mg +MTX minus PBO+MTX.			
Revised from sponsor Table 11:15, page 115 of 6142; Source Table 14.2.3:1.			

Health-Related Quality of Life, SF-36 – Study 050

Regardless of the dose regimen, CZP + MTX treated patients reported greater improvements compared to PBO + MTX in HRQoL assessed by the SF-36 physical component summary (PCS) and mental component summary (MCS). The PCS score of the Medical Outcomes Survey 36-Item Short Form (SF-36) was used as a secondary endpoint to support the improvement in physical function claim. Patients in both active treatment groups experienced improvements in HRQoL across all assessments in the SF-36 PCS and MCS by a statistically greater change in the active treatment groups compared to the PBO + MTX treatment group ($p<0.001$). See **Table 68.** In addition, the primary analysis for the supportive secondary endpoint (SF-36, PCS) demonstrated improvements with the LOCF imputation from week 12 through week 24 ($p<0.001$).

In an additional pre-specified analysis (comparison of the change from Baseline in SF-36, PCS and MCS scores, at Weeks 12 and 24 - repeated analysis - direct likelihood) for both the PCS and MCS at Week 12, the improvements in HRQoL were greater in the CZP treatment groups compared to the PBO + MTX group (p<0.001). At Week 24 only for the PCS, the repeated analysis demonstrated greater improvements for the CZP treated patients (p=0.032 and p=0.057 for CZP 200 mg and CZP 400 mg + MTX, respectively). The MCS results were not statistically significant.

In summary, the results of the secondary efficacy endpoints, physical function and disability, assessed by the HAQ-DI and supported by the SF-36 and their sensitivity analyses, supported the proposed claim for improvement in physical function for CZP treated patients compared to PBO treated patients. The Agency has granted claims for improved physical function based on the HAQ-DI, with supportive SF-36/PCS outcomes in RA patients. The MCS has not been validated in patients with RA and, therefore, does not provide adequate evidence to grant a claim.

Table 68. Change from Baseline in SF-36, Physical and Mental Component – Study 050

Change from Baseline in SF-36, PCS and MCS, Summary Scores at Week 24 - Study 050 (LOCF) ITT Population			
Week 24 / Component	PBO+MTX N = 127	CZP 200 mg sc q2w + MTX N =246	CZP 400 mg sc q2w + MTX N =246
Physical Component Summary (PCS)			
n	123	238	240
Baseline, Mean (SD)	31 (7)	31 (6)	31 (6)
Change from Baseline at Week 24			
Adj. Mean (SE) [a.]	0.9 (1)	5 (1)	5 (1)
p-value		<0.001	<0.001
Mental Component Summary (MCS)			
Baseline, Mean (SD)	40 (11)	39 (11)	40 (11)
Change from Baseline at Week 24			
Adj. Mean (SE) [a.]	1.2 (10)	6 (10)	6 (11)
p-value		<0.001	<0.001

"n" for the MCS are the same as reported for PCS.
(a.) ANCOVA with region and treatment as factors and Baseline as covariate.
Abbreviations: SD=standard; MTX=methotrexate. Revised from sponsor Table 11:16, p 117 of 6142.

Tiredness (Fatigue) – Study 050

Tiredness was measured with the Fatigue Assessment Scale (FAS), a numerical scale assessing tiredness, weariness as components of fatigue. The SF-36 Vitality Domain was employed to support the FAS results. See **Table 69.**

Although both CZP treatment groups demonstrated statistically significantly greater reductions in tiredness (fatigue) than the PBO + MTX treatment group (p<0.010) at all time-points, (b) (4)

Table 69. Comparison of Change from Baseline in the Fatigue Assessment Scale, Study 050

Comparison of Change from Baseline in Fatigue Assessment - Study 050			
LOCF (ITT Population)			
Timepoint	PBO+MTX N = 127	CZP 200 mg sc q2w + MTX N = 246	CZP 400 mg sc q2w + MTX N = 246
Baseline Visit, Mean (SD)	6.5 (2)	6.7 (2)	6.4 (2)
Week 6, Mean (SD)	-0.4 (2)	-1.7 (2)	-1.5 (2)
Week 12, Mean (SD)	-0.4 (2)	-1.7 (2)	-1.8 (2)
Week 24, Mean (SD)	-0.5 (2)	-2.1 (2)	-2 (0)

Revised from sponsor Table 14.5.2:15, page 4142 to 4145 of 6142

Work Productivity Survey (WPS) – Study 050
The WPS assessed the impact of arthritis on a patient's productivity, within and outside the home, over the previous 4 weeks. Overall, improvement in productivity, within and outside the home, was seen by Week 4 and maintained through Week 16 in both active treatment groups compared to the PBO + MTX treatment group. After Week 16, the comparison was difficult to adequately assess due to the high rate of dropout in the PBO group.

See comments about the WPS under Section 6.1.5, Study 027, page 90 of this review.

6.2.6 Other Endpoints – Study 050

The DAS28(ESR), the DAS28(ESR) Remission, EULAR Response and the ESR were additional secondary endpoints employed to support the primary efficacy endpoint, the ACR responder criteria and each of these additional endpoints achieved a positive result. The Time to withdraw Due to Lack of Efficacy, Euro Qol-5D Health State Evaluation and the Healthcare Resource Utilization Questionnaire each showed favorable outcome for the active treatment groups compared to the PBO + MTX group, therefore supporting the primary efficacy outcome. The Changes in RA Concomitant Medication did not show any significant differences across the treatment arms.

DAS28(ESR) – Study 050
The DAS28(ESR) is a clinical index of RA disease activity that combines variables of arthritis as well as of general health in patients with RA. Both CZP treatment groups showed a statistically significantly greater improvement at all time points in the change from Baseline for the DAS28(ESR) compared to PBO + MTX ($p<0.001$).

DAS28(ESR) Remission – Study 050
DAS28(ESR) remission (DAS28 < 2.6) is used to assess remission based on a low value of DAS28. At Week 24, both active treatment groups showed a statistically significant benefit compared to PBO + MTX ($p=0.014$ for CZP 200 mg + MTX and $p=0.017$ for CZP 400 mg + MTX).

EULAR Response – Study 050
The European League against Rheumatism (EULAR) response criteria uses the individual change in the DAS and the level of DAS achieved to classify trial participants as good, moderate or non-responders. From Week 12 through Week 24, there was a statistically significant

difference in favor of both active treatment groups compared to PBO + MTX for a EULAR good response (p=0.005 for CZP 200 mg + MTX and p=0.006 for CZP 400 mg + MTX).

Erythrocyte Sedimentation Rate – Study 050
At Week 24, both CZP groups demonstrated a statistically significant difference in the ratio to Baseline in the ESR (decrease in ESR) compared to PBO + MTX (p<0.001 for CZP 200 mg and 400 mg + MTX).

Time to withdraw Due to Lack of Efficacy – Study 050
The number of patients who withdrew due to lack of efficacy in Study 050 was less in the CZP 200 mg and 400 mg + MTX groups (23% and 22%, respectively) than in the PBO + MTX group (84%). A similar favorable trend was also observed in Study 027 supporting the primary efficacy endpoint.

Changes in RA Concomitant Medication – Study 050
All patients in Study 050 were taking concomitant MTX at Baseline, as per the protocol. Paracetamol was the only concomitant medication that was added by more than 2 patients per treatment group. Overall, there were no significant changes in concomitant medication across the treatment groups.

Euro Qol-5D Health State Evaluation – Study 050
The EQ-5D was an exploratory endpoint assessed in European patients only (n=554). The health state assessed by the VAS showed an improvement over time up to Week 24 in both CZP + MTX treatment groups (mean scores improved by 17 points in CZP 200 mg + MTX, by 16.9 points in CZP 400 mg + MTX group at Week 24 compared to 1.6 points in the PBO + MTX group).

Healthcare Resource Utilization Questionnaire – Study 050
The HCRU questionnaire provided an assessment of healthcare resource utilization and was employed as an exploratory efficacy endpoint. The Agency does not employ health care utilization data in support of the treatment of signs and symptoms of RA. Therefore, this endpoint was not used to support the proposed indication.

Subgroup Analysis of ACR20 Responder Rate at Week 24 –Study 050
The CZP RA clinical development program was global in scope. In order to determine whether the treatment effect was consistent across different countries and subgroups, we examined treatment-by-factor interactions for the primary efficacy endpoint (ITT population). As pre-specified in the protocol for the subgroup analyses, tests for 2-factor interactions between treatment and the subgroups were assessed for statistical significance at the 0.10 level.

Table 70 shows an analysis of the ACR20 responder rates at Week 24 in selected subgroups analyses. Of note, patients taking MTX < 15 mg/wk trended with a higher ACR20 responder rate (61% and 61%, CZP 200 mg and 400 mg groups, respectively, compared, interestingly, to those patients taking MTX ≥ 15 mg/wk, 49% and 52%, CZP 200 mg and 400 mg groups, respectively).

Overall, the treatment effect of CZP was consistent across the subgroups. Irrespective of age, gender, race, weight, BMI, disease duration, MTX dose, corticosteroid use, previous anti-TNF or DMARD use, DAS28(ESR) class, CRP, ESR, RF status, anti-CZP antibody status, region, nation or protocol version, both active treatment groups as measured by the ACR20 at 24 Weeks demonstrated consistent support of the primary efficacy endpoint results favoring the active treatment groups compared to the PBO treatment.

Table 70. Comparison of ACR20 Responder Rate at Week 24, Subgroup Analyses – Study 050

Comparison of ACR20 Responder Rate at Week 24 -Select Subgroup Analyses (ITT population) - Study 050			
	PBO + MTX	CZP 200 mg q2w + MTX	CZP 400 mg q2w + MTX
Age group < 65 yrs at Baseline, (n)	112	213	203
Responder	8 (7%)	123 (58%)	117 (58%)
Age group ≥ 65 yrs at Baseline, (n)	15	33	42
Responder	3 (20%)	18 (55%)	24 (57%)
Male at Baseline, (n)	20	40	54
Responder	0	18 (45%)	29 (54%)
Female (n)	107	206	191
Responder	11 (10%)	123 (58%)	112 (59%)
Disease Duration ≤ 3 yrs. at Baseline (n)	41	74	72
Responder	3 (7%)	39 (53%)	36 (50%)
Disease Duration > 3 yrs. at Baseline (n)	86	172	173
Responder	8 (9%)	102 (59%)	105 (61%)
MTX Dose < 15mg/wk at Baseline (n)	91	171	160
Responder	7 (8%)	104 (61%)	97 (61%)
MTX Dose ≥ 15mg/wk at Baseline (n)	36	75	85
Responder	4 (11%)	37 (49%)	44 (52%)
Steroid Use, Yes, at Baseline, (n)	76	136	151
Responder	7 (9%)	80 (59%)	86 (57%)
Steroid Use, No, at Baseline, (n)	51	110	94
Responder	4 (8%)	61 (56%)	55 (59%)
Previous anti-TNF Use, Yes, at Baseline, (n)	6	9	15
Responder	1 (17%)	8 (89%)	10 (67%)
Previous anti-TNF Use, No, at Baseline (n)	121	237	230
Responder	10 (8%)	133 (56%)	131 (57%)
RF Negative [(d.)] at Baseline (n)	27	54	58
Responder	2 (7%)	30 (56%)	26 (49%)
RF Positive [(d.)] at Baseline (n)	97	186	179
Responder	9 (9%)	109 (59%)	112 (63%)

(a) Wald p-value for the comparison of the treatment groups have been calculated using logistic regression with factors for treatment, subgroup, region and subgroup by treatment interaction.
(b) Odds ratio: CDP870/placebo calculated using logistic regression with factors for treatment, subgroup, region and subgroup by treatment interaction.
(c) Odds ratio: CDP870 400mg/CDP870 200mg calculated using logistic regression with factors for treatment, subgroup, region and subgroup by treatment interaction. NP = Not presented as this category of the subgroup contains less than 15% of the total number of patients. NC = Not calculated due to separation of data.

Comparison of ACR Response by Anti-CZP Antibody Status – Study 050

The ACR20 response at Week 24 was analyzed against the antibody status of patients in Study 050. The overall incidence of antibody positive results, among patients with antibody data, increased from Week 4 (0.2%) to Week 24 (3%). It is important to note that the detection of anti-

CZP antibodies can be hampered by the presence of CZP in the plasma, which, in turn, may lead to false-negative results and to an underestimation of the incidence of antibody production.

When the Week 12 follow-up samples were included, the overall percentage of patients who tested positive to anti-CZP antibodies was 6% (29 of 494 patients: 10% [24/248] in the CZP 200 mg + MTX group and 2% [5/246] patients in the CZP 400 mg + MTX group). Overall, at any time, the incidence of antibody positive patients was higher in the CZP 200 mg + MTX treatment group (9%) compared to the CZP 400 mg + MTX treatment group (2%). There appears to be increased likelihood of developing anti-CZP antibody with the CZP 200 mg q2w + MTX dose regimen compared with the CZP 400 mg q2w + MTX dose regimen. See **Table71.** See Clinical Pharmacology review by Christoffer Tornoe, PhD and Srikanth Nallani, PhD.

Table 71. Anti-CZP Antibody Status by Treatment Group – Study 050

Summary of Anti-CZP Antibody Detection by Treatment Group - Study 050			
Safety Population			
	CZP 200 mg q2w + MTX N = 248	CZP 400 mg q2w + MTX N =246	All CZP Doses N = 494
Overall, any Ab+	21 (8.5%)	4 (1.6%)	25 (5.1%)
Week 24, Ab+ [b.]	6 (3.5%)	3 (2%)	9 (3%)
Last/Withdrawal, Ab+ [b.]	15 (6%)	3 (1%)	18 (4%)
Antibody+ and antibody - status based on maximum antibody level during the treatment period, excluding the 12-week follow-up samples. (b.) Antibody, Ab+, level > 2.4 U/mL; antibody negative, ab-, ≤ 2.4 U/mL. Revised from sponsor Table 14.3.10:2, page 4002 of 6142.			

Table 72 shows an analysis of responses in antibody-positive and antibody-negative patients. As noted above, antibody positivity was more frequent in the CZP 200 mg q2w group than in the CZP 400 mg q2w group (8% versus 2%, respectively). In the CZP 200 mg q2w group, fewer antibody-positive patients had an ACR20 response compared with antibody-negative (35% versus 59%), respectively. The frequency of antibody positivity was too small in the 400 mg q4w group to reach a conclusion. The labeling would need to inform prescribing physicians of the observed reduced frequency of ACR20 response associated with the development of anti-CZP antibody

Table 72. Comparison of ACR20 Responder Rate by Antibody Status at Week 24 – Study 050

Comparison of ACR20 Responder Rate by Antibody Status, Week 24 - Study 050 (ITT)				
	CZP 200 mg q2w + MTX N = 246		CZP 400 mg q2w + MTX N = 246	
Week 24	Ab -	Ab +	Ab -	Ab +
n (%)	226 (92%)	20 (8%)	241 (98%)	4 (2%)
Responder	134 (59%)	7 (35%)	139 (58%)	2 (50%)

Treatment by subgroup interaction [a.], p=0.854.
Abbbreviations: Ab=antibody; ITT=intent-to- treat population; MTX=methotrexate.
(a.) Wald p-values for the comparison of the treatment groups were calculated using logistic regression with factors for treatment, subgroup, region and subgroup by treatment interaction. Revised from sponsor Table 11:23, page 136 of 6142

6.2.7 Subpopulations – Study 050

The relevant subpopulations are discussed as subgroups under the secondary efficacy endpoint section of this review.

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations – Study 050

The dose finding studies across the CZP RA development program are adequate. Study 050 employed the commercially intended liquid CIMZIA® formulation and supports CZP 200 mg q2w + MTX and CZP 400 mg q2w + MTX in patients with RA. The primary efficacy endpoint results as measured by the ACR20 response at 24 weeks are similar across the two dose regimens. Therefore, the proposed dosage and administration for adults with CZP 400 mg subcutaneously initially at Week 0, 2 and 4 followed by the maintenance dose of CZP 200 mg q2w (+ MTX) is acceptable. See the labeling recommendations in the APPENDICES, Section 9.2 of this review.

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects – Study 050

Both dose regimens of CZP 200 mg and 400 mg q2w + MTX achieved an ACR20 response at Week 12 and 24 demonstrating persistence of efficacy over time. This outcome in Study 050 supports the co-primary efficacy endpoint the ACR20 response outcome in Study 027 at Week 12 and 24. There was no evidence of the loss of tolerance in Study 050 because the efficacy persisted through week 24.

6.2.10 Additional Efficacy Issues/Analyses –Study 050

All efficacy analyses are included in the appropriate subsections of Section 6.0 Review of Efficacy.

6.2.11 Summary of Efficacy – Study 050

Study 050 employed the commercially intended liquid formulation of CIMZIA® and was global in the scope of clinical sites. The result of the primary efficacy analysis, the ACR20 response at Week 24, was statistically significant and clinically meaningful for CZP 200 mg and 400 mg q2w + MTX for the proposed treatment of the signs and symptoms of RA. In Study 050, the major secondary efficacy endpoint at week 24, inhibition of progression of structural damage as measured by mTSS, achieved statistically significant differences as measured by mTSS, erosion scores and joint space narrowing scores (JSN) in both CZP groups compared with the PBO + MTX group. The percent of patients with no radiographic progression was 71%, 77% and 58% in the CZP 200 mg, 400 mg + MTX and PBO + MTX treatment groups, respectively. Significant differences in the inhibition of progression of structural damage at Week 24 was achieved by the mean change from Baseline in mTSS at Week 24: 0.2 vs 1.2 for the CZP 200 mg + MTX group vs PBO + MTX group, respectively ($p=0.003$). For the CZP 400 mg + MTX group, a negative value of -0.4 was achieved ($p<0.001$).

The cumulative probability plot of radiographic change in Study 050 showed that fewer patients had large amount of progression in radiographic damage with the CZP 400 mg dose regimen compared to the CZP 200 mg dose regimen with extended treatment. In contrast, the cumulative probability plot for Study 027 showed similar results for CZP 400 mg and 200 mg employing the same CZP dose regimens with the lyophilized formulation of CIMZIA®.

The percentage inhibition of the progression of structural damage compared with PBO + MTX was greater than 80% for both CZP dose regimens at Week 24. Overall, both CZP dose regimens showed inhibition of progression of structural damage as measured by mTSS, and these outcomes were similar to the radiographic outcomes in Study 027 at Week 24.

All of the secondary efficacy endpoints supported the primary analysis. The ACR20 response was achieved at Week 1 and maintained through Week 24 for CZP 200 mg (57%) and CZP 400 mg (58%) groups compared to the PBO + MTX (9%) group. The pre-specified sensitivity analyses supported the primary analysis in both CZP treatment groups for each of the endpoints. All components of the ACR response demonstrated improvement from Baseline in the active treatment groups compared to the PBO + MTX group at Week 24.

In both CZP treatment groups, significant improvements in physical function were shown by the HAQ-DI and supported by the Physical Component Summary (PCS) of the SF-36 compared to PBO + MTX treatment group.

Overall, both CZP treatment groups showed a consistent effect for comparison of the ACR20 responder rate across the subgroup analyses. The lower dose regimen, CZP 200 mg q2w + MTX, showed a higher incidence of anti-CZP antibody formation compared to CZP 400 mg q2w + MTX regimen. In addition, there appears to be a trend toward decreased efficacy, as measured by the ACR20 response, with increased anti-CZP antibody levels. This trend has been reported with other TNF-inhibitor agents.

Overall, the treatment effect of CZP was consistent across the subgroups of age, gender, race, weight, BMI, disease duration, corticosteroid use, previous anti-TNF or DMARD use, DAS28 (ESR) class, CRP, ESR, region, nation or protocol version, both active treatment groups as measured by the ACR20 at 24 Weeks and demonstrated support of the primary efficacy endpoint results favoring both CZP dose regimens compared to the PBO group. Study 050 demonstrated treatment effects with CZP 200 mg and 400 mg q2w + MTX that were comparable to those seen with other anti-TNF products.

6.3 Indication – Study 014

The proposed indication in Study 014 is the same as reported in Study 027 and 050.

6.3.1 Methods – Study 014

The efficacy contained in Section 6.3 of this review was generated from Study CDP870-014 (Study 014). Study 014 was a 24 Week, randomized, placebo-controlled study of CZP 400 mg

q4w + MTX. The analyses of the primary efficacy endpoint, the ACR20 response at Week 24, and the various secondary efficacy endpoints, as well as the analyses of the exploratory efficacy endpoints, were examined for Study 014. All of the primary and selected secondary efficacy endpoint analyses were confirmed by the FDA's statistical reviewer, Katherine Meaker, PhD. See Section 5.3 Discussion of Individual Studies for the protocol review.

6.3.2 Demographics – Study 014

The patient population was well balanced across the two treatment groups, CZP 400 mg q4w + MTX and PBO + MTX, in the demographic, Baseline characteristics, history of RA disease and extra-articular features of RA at Baseline. The mean age of patients was 54 years of age. The majority of patients were female and Caucasian (69% and 99%, respectively). See **Table 73.**

Table 73. Demographic and Baseline Characteristics – Study 014

Demographic and Baseline Characteristics - Study 014 and History of Rheumatoid Arthritis (All randomized patients)			
	PBO + MTX N = 121	CZP 400 mg sc q4w + MTX N = 126	Overall N = 247
Age (yrs) Mean (SD)			
Mean (SD)	56 (12)	53 (13)	54 (12)
Gender			
Male	40 (33%)	35 (28%)	75 (30%)
Female	80 (66%)	91 (72%)	171 (69%)
Race			
Caucasian	119 (98%)	126 (100%)	245 (99%)
Asian	1 (1%)	0	1 (0%)
Unknown	1 (1%)	0	1 (0%)
Duration of Disease (yrs.)			
Mean (SD)	10 (8)	9 (8)	
Median [range]	7.7 [1, 33]	7.7 [1, 43]	
Rheumatoid Factor			
Positive	95 (79%)	93 (74%)	
Negative	22 (18%)	31 (25%)	
Concomitant MTX Dose			
Mean (SD)	17 (4)	17 (4)	
Median Dose [range]	15 [10, 25]	15 [10, 25]	
Abbreviations: yrs.=years; SD=standard deviation; PBO=placebo' MTX= methotrexate. Revised from sponsor Table 11:1 and 11:2, page 106 and 107 of 6006.			

Baseline ACR Components – Study 014

Overall, there were no clinically meaningful differences between treatment groups for the tender/painful joint count, swollen joint count, Patients' Global Assessment of Arthritis, Physician's Global Assessment of Arthritis, Patient's Assessment of Arthritis Pain, HAQ-DI, CRP, and DAS28. See **Table 74.**

Table 74. Baseline values for the ACR Components – Study 014

Baseline Values for ACR Components - Study 014 (All randomized patients)			
	PBO + MTX (N = 121)	CZP 400 mg sc q4w + MTX (N = 126)	Overall (N = 247)
Tender/painful joint count Mean (SD)	31 (13)	29 (12)	30 (12)
Swollen joint count Mean (SD)	22 (10)	23 (9)	23 (9)
Patient's Global Assessment of Arthritis, Mean (SD)	3.3 (0.66)	3.3 (0.68)	3.3 (0.67)
Physician Global Assessment of Arthritis, Mean (SD)	3.5 (0.61)	3.6 (0.64)	3.6 (0.62)
Patient's Assessment of Arthritis Pain (0-100 mm VAS), Mean (SD)	60 (19)	57 (21)	59 (20)
HAQ-DI Mean (SD)	1.5 (0.65)	1.4 (0.63)	1.4 (0.63)
ESR Geometric mean (95%CI)	26	24	25
Median (range)	29 (3, 110)	28 (1, 150)	28 (1, 150)
C-Reactive Protein (CRP) mg/L Geometric mean (95%CI)	13 (11, 15)	12 (10, 14)	12 (11, 14)
Abbreviations: SD=standard deviation; PBO=placebo; MTX=methotrexate; Revised from sponsor Table 11:4, pages 109-110 of 6006 and Table 14.1.3:4, pages 320-326 of 6006.			

Concurrent Medications – Study 014

Overall, there were no significant differences between the treatment groups in the proportion of patients taking concomitant medications or the prior use of arthritis medications. See **Table 75.** The most frequent concomitant medication used was MTX (pre-specified in the protocol) and was taken by more than 98% of patients. Other concomitant medications used by more than 10% of patients in either group included prednisolone, diclofencac, celecoxib, prednisone, rofecoxib, methyl- prednisolone, alendronic acid, paracetamol, levothyroxine and omeprazole. Patients with MTX use that did not meet the specifications of the protocol were identified as having protocol violations during the blinded review of deviations/ violations and were excluded during the sensitivity analyses. As demonstrated in **Table 76**, there were a minimal number of patients who had been exposed to prior biologic therapies, the most common being anakinra.

Table 75. Concurrent Medications at Baseline Taken by ≥ 5% of Patients – Study 014

Concurrent Medications at Baseline Taken by ≥ 5% of Patients - Study 014 (All randomized patients)		
Medication	**PBO + MTX (N = 121)**	**CZP 400 mg sc q 4w + MTX (N=126)**
# of patients with ≥ 1 concomitant medication at Baseline		
Methotrexate	117 (97%)	126 (100%)
Prednisolone	33 (27%)	35 (28%)
Diclofenac	25 (21%)	22 (18%)
Prednisone	21 (17%)	21 (17%)
Rofecoxib	18 (15%)	19 (15%)
Methylprednisolone	14 (12%)	15 (12%)
Paracetamol	17 (14%)	12 (10%)
Omeprazole	12 (10%)	8 (6%)
Meloxicam	4 (3%)	8 (6%)
Tramadol	10 (8%)	7 (6%)
Naproxen	8 (7%)	5 (4%)
Abbreviations: PBO=placebo; MTX=methotrexate. Revised from sponsor Table 11:6, page 112 of 6006.		

Table 76. TNF Inhibitors and Other biological Medications – Study 014

Anti-TNF Inhibitors and Other Biologic Prior Medications for RA - Study 014 (All randomized patients)		
Medication	PBO + MTX (N = 121)	CZP 400 mg sc q4w + MTX (N=126)
Anakinra	2 (2%)	7 (6%)
Infliximab	1 (1%)	0
Interferon	1 (1%)	0
Revised from sponsor Table 14.1.5:1, pages 384 to 389 of 6006.		

6.3.3 Patient Disposition – Study 014

A total of 247 patients were randomized in a ratio of 1:1 (across 43 centers in 7 countries) to receive PBO + MTX (121 patients) and CZP 400 mg q4w + MTX (126 patients), respectively. See **Table 77.** Of the 247 total randomized patients, 243 received at least one dose of study medication and were included in the modified intent-to-treat (mITT) population. There were 163 patients (66%) who completed Study 014 at Week 24. Of the 121 patients who received PBO + MTX, 65 (54%) were considered completers and, of the 126 patients who received CZP 400 mg + MTX, 98 (78%) were considered completers.

A total of 84 (34%) patients withdrew from Study 014, of whom 56 (46%) received PBO + MTX and 28 (22%) received CZP 400 mg + MTX. The most frequent reason for withdrawal was lack of efficacy in 45 (37%) patients in the PBO + MTX group and 16 (13%) of patients in the CZP 400 mg + MTX group and was AEs in 8 (7%) of patients in the PBO + MTX group and 7 (6%) of patients in the CZP 400 mg + MTX group.

The largest number of patients withdrew between Week 12 and Week 16 (28 patients [27 non-responders] and Week 16 and Week 20 (28 patients [26 non-responders]). This finding most likely reflects the option of patients to enter the open-label (OL) Study 015 after completing a minimum of 12 weeks of treatment in Study 014. Similar effects of early withdrawal were observed in Study 027 and 050 also due to the study design option of a patient being able to enter an open-label study between week 12 and 16.

Table 77. Patient Disposition – Study 014

Patient Disposition - Study 014 (All randomized patients)			
	PBO + MTX N = 121	CZP 400 mg sc q4w + MTX N = 126	Overall N = 247
Randomized but did not take CZP dose	2 (2%)	2 (2%)	4 (2%)
Randomized (ITT population)	121	126	247
Randomized (mITT and safety pop.)	119 (98%)	124 (98%)	243 (98%)
Completed at Week 24	65 (54%)	98 (78%)	163 (66%)
Withdrawals	56 (46%)	28 (22%)	84 (34%)
Discontinued due to AEs	8 (7%) [a]	7 (6%)	13 (5%)
Lack of efficacy	45 (37%)	16 (13%)	61 (25%)
Deaths	0	0	0
Protocol violations	0	1 (1%)	1 (0.4%)
Lost to follow-up/Unknown	2 (2%)	2 (2%)	4 (2%)
Consent withdrawn	3	2	5
Completed study per protocol	79 (66%)	92 (73%)	171 (69%)
Pts with non-missing data for the primary efficacy endpoint [b]	91%	91%	91%

Proportion of Patients Randomized by Country – Study 014

The CZP RA clinical development program was global in scope. Study 014 was conducted in 43 centers in the following 7 countries: Austria (2 sites), Belgium (5 sites), Czech Republic (5 sites), Germany (10 sites), Ireland (4 sites), USA (4 sites), and the United Kingdom (13 sites). The number of patients randomized by country is shown in **Table 78.**

Table 78. Patients Randomized by Country – Study 014

Patients Randomized by Country - Study 014 (All randomized patients)			
Country	PBO + MTX (N = 121)	CZP 400 mg sc q4w + MTX (N = 126)	Overall (N = 247)
Germany	49	47	96
United Kingdom	23	23	46
Czech Republic	17	22	39
USA	12	13	25
Austria	9	9	18
Belgium	6	7	13
Ireland	5	5	10
Revised from sponsor Table 10:1, page 100 of 6006.			

6.3.4 Analysis of Primary Endpoint – Study 014

ACR Response – Study 014

The primary efficacy endpoint analysis in Study 014 was the ACR20 response at Week 24 in the mITT population. A patient was considered a "responder" if he/she me the criteria of ACR20 improvement over Baseline at Week 24. Any patient who withdraws from the study at nay time during the study for any reason will be considered a non-responder. There was a statistically significant difference ($p<0.001$) between the PBO + MTX patients and the CZP 400 mg q4w + MTX patients favoring the CZP 400mg therapy. See **Table 78.** At Week 24, there were 27 (23%)

and 56 (46%) of patients who were ACR20 responders in the PBO + MTX group compared to the CZP 400 mg q4w + MTX group, respectively.

Sensitivity analyses – ACR0 Response – Study 014
The pre-specified sensitivity analyses were based on the mITT population at Week 24 and supported the primary efficacy analyses. There were 32 (27%) and 59 (48%) of patients as ACR20 responders in the PBO + MTX group compared to the CZP 400 mg + MTX group at Week 24 ($p<0.001$). The pre-specified sensitivity analyses also included an analysis excluding protocol violators or CZP 400 mg + MTX treated protocol violators. See **Table 78.**

In the pre-specified sensitivity analysis based on LOCF, the CZP 400 mg q4w + MTX group demonstrated a higher ACR20 response compared to the PBO + MTX group with the differences shown as early as Week 1 and through Week 24. See **Table 79** and **Figure 12.**

Table 78. Primary Endpoint Analysis and Sensitivity Analyses, ACR20 Response – Study 014

ACR20 Response at Week 24 - Study 014			
Sensitivity Analysis (mITT)			
	PBO + MTX N = 119	CZP 400 mg sc q4w + MTX N = 124	p-Value [a.]
Responder [b.]	32 (27%)	59 (48%)	<0.001
Sensitvity Analysis - Excuding Protocol Violators (mITT)			
Responder [b.]	21 (27%)	45 (50%)	0.002
Sensivity Analysis - Excluding CZP Treated Protocol Violators (mITT)			
Responder [b.]	27 (23%)	45 (50%)	<0.001

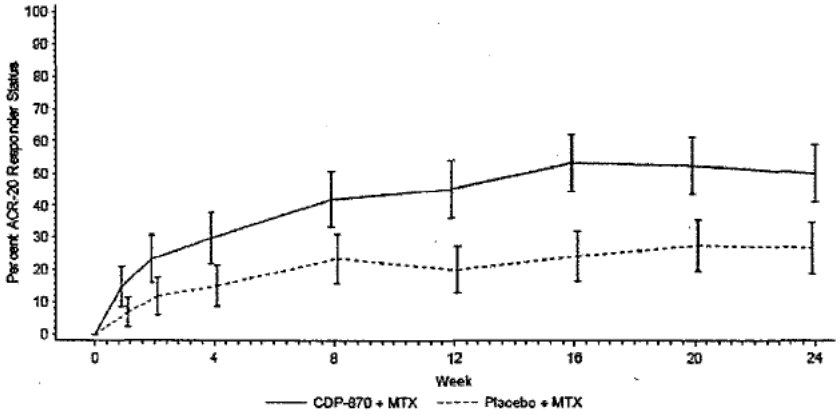
(a.) Cochran-Mantel-Haenszel (CMH) test of treatment comparison stratified by country.
(b.) A patient was considered a responder if he/she met the criteria for ACR20 improvement over Baseline at Week 24. Any patient who withdrew was considered a non-responder.
Abbreviations: PBO=placebo; MTX=methotrexate; mITT= modified intent-to-treat.
Revised from sponsor Table 14.2.1:2, page 443 of 6006.

Table 79. ACR20 Response Analyzed by LOCF – Study 014

ACR20 Response Analyzed by LOCF (mITT) - Study 014			
	PBO + MTX N = 199	CZP 400 mg sc q4w + MTX N = 124	p-value [a.]
Week 12, responders	24 (20%)	56 (45%)	<0.001
Week 16, responders	29 (24%)	66 (53%)	<0.001
Week 24, responders	32 (27%)	62 (50%)	<0.001

(a.) CMH test of treatment comparison stratified by country. Revised from sponsor Table 11:11, page 118 of 6006

Figure 12. ACR20 Response (LOCF) Percent Response [95%CI] over Time by Treatment Group (mITT) Sponsor Figure 11.1, page 118 of 6006.



Overall, the analysis of the primary efficacy endpoint, the ACR20 responders at Week 24 in the mITT population, demonstrated statistical significant improvement for the CZP 400 mg q4w + MTX treatment group compared to the PBO + MTX treatment group.

6.3.5 Analysis of Secondary Endpoint(s) – Study 014

ACR50 Response – Study 014

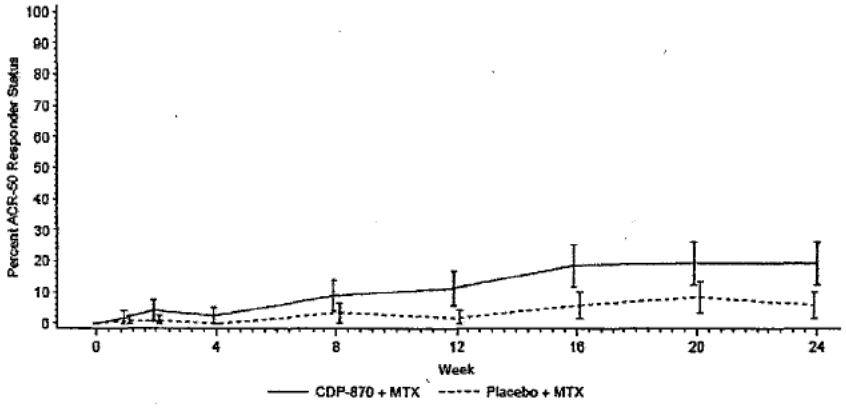
The secondary efficacy endpoint, the ACR50 response at Week 24, supported the primary efficacy outcome of the ACR20 response at Week 24 with a statistically significant difference favoring the CZP 400 mg group (p=0.004). There were 22 (18%) and 7 (6%) of patients in the CZP 400 mg q4w + MTX compared to the PBO + MTX group who were ACR50 responders. See **Table 80** and **Figure 12.**

Table 80. ACR50 and ACR70 at Week 24 – Study 014

ACR50 and ACR70 at Week 24 - Study 014 (mITT)			
	PBO + MTX (N=119)	CZP 400 mg q4w + MTX (N=124)	p-value [a.]
ACR-50			
Week 24, Responder	7 (6%)	22 (18%)	0.004
ACR-70			
Week 24, Responder	2 (2%)	0	0.133

(a.) CMH test of treatment comparison stratified by country. Responders were defined as at least 50% improvement from Baseline in the number of tender/painful joints and in the number of swollen joints as well as at least a 50% improvement in at least 3 of the following 5 assessment: Physician's Global, Patient's of arthritis pain, CRP, or HAQ-DI. Revised from sponsor Table 14.2.3:1, page 507 of 6006.

Figure 12. ACR50 Response (LOCF) Percent Response (95% CI) over Time by Treatment Group (mITT) – Study 014



ACR70 Response – Study 014

There were only two patients who achieved an ACR70 response and both of these patients were in the PBO + MTX group.

Change from Baseline for Individual ACR Components – Study 014

Overall, each of the change from Baseline in the individual components of the ACR supported the primary efficacy analyses in Study 014. See **Table 81.**

Table 81. Change in the Individual Components of the ACR – Study 014

Mean Change from Baseline - ACR Components - Study 014 Week 24 (mITT)		
	PBO + MTX N = 121	CZP 400 mg sc q4w + MTX N = 126
Tender Painful Joint Count		
Baseline Mean (SD)	31 (12.91)	29 (11.63)
Week 24, LS Mean Change	-6	-15
Swollen Joint Count		
Baseline, Mean (SD)	22 (10)	23 (9)
Week 24, LS Mean Change	-6	-13
Patient's Global Assessment of Arthritis		
Baseline Mean (SD)	3.3 (0.66)	3.3 (0.68)
Week 24, LS Mean Change	-0.3	-0.6
Physician's Global Assessment of Arthritis		
Baseline Mean (SD)	4	4
Week 24, LS Mean Change	-0.5	-1.1
Patient's Assessment of Arthritis Pain (VAS)		
Baseline Mean (SD)	60	56
Week 24, LS Mean Change	-9	-22
Health Assessment Questionnaire - Disease Index (HAQ-DI)		
Baseline Mean (SD)	1.5	1.4
Week 24, LS Mean Change	1.38	1.12
C-Reactive Protein (CRP) (mg/mL) [a.]		
Baseline Geo. Mean (95% CI)	13.1 (11-15)	11.7 (10 -14)
Week 24, Geo. Mean (95% CI)	11.7 (10 - 14)	7.2 (6 - 8)
Erythrocyte Sedimentation Rate (ESR)		
Baseline Geo. Mean (95% CI)	26 (22, 30)	24 (21, 28)
Week 24, Geo. Mean (95% CI)	27 (22, 31)	17 (17, 20)
Revised from sponsor Table 14.2.4:1, page 541 of 6006; Table 14.2.5:1, from page 547 of 6006; Table 14.2.6:1, page 554 of 6006; Table 14.2.7:1, page 563 of 6006; Table 14.2.8:1, page 572 of 6006; Table 14.2.9:1, page 579 of 6006; Table 14.2.10:1, page 585 of 6006;Table 14.2.11:1, p. 591 of 6006. (a.) The CRP data is based on the last observation carried forward approach.		

6.3.6 Other Endpoints – Study 014

Plasma Concentrations of CZP – Study 014
Overall, there did not appear to be any meaningful differences between ACR20 responders and ACR20 non-responder patients with respect to the CZP plasma concentrations over time. See the Clinical Pharmacology review by Christoffer Tornoe, PhD and Srikanth Nallani, PhD.

Comparison of ACR Responder Rate by Anti-CZP Antibody Status - Study 014
Two patients (2%) with detectable anti-CZP antibodies were first observed at Week 8 and the maximum number of patients with detectable anti-CZP antibodies was at Week 20, a total of 4 patients (4%). Overall, including the follow-up assessment at 12-Week post final dose, there were 5 (4%) patients with detectable anti-CZP antibodies in Study 014. See **Table 82.**
Overall, there were too few patients with anti-CZP antibodies to allow a meaningful analysis of CZP concentrations by anti-CZP antibody status or for any meaningful analysis of the ACR20/50/70 response by anti-CZP antibody.

Table 82. Incidence of Anti-CZP Antibody formation – Study 014

Anti-CZP Antibody Status - Study 014 (All randomized patients)		
	CZP 400 mg sc q4w + MTX (N = 126)	
	Antibody Negative [a] Antibody level ≤ 2.4 U/mL	Antibody Positive [a] Antibody level > 2.4 U/mL
Week 8	118 (98%)	2 (2%)
Week 12	105 (99%)	1 (1%)
Week 16	99 (98%)	2 (2%)
Week 24	114 (98%)	2 (2%)
Overall [b]	119 (96%)	5 (4%)

(a.) Antibody level > 2.4 U/mL; Antibody level ≤ 2.4 U/mL.
(b.) Antibody status based on maxium antibody level during the 24 Week treatment period of Study 014.
Revised from sponsor Table 14.3.9:1, page 1229 of 6006.

6.3.7 Subpopulations – Study 014

The relevant subpopulations are discussed as subgroups under the secondary efficacy endpoint section of this review.

6.3.8 Analysis of Clinical Information Relevant to Dosing Recommendations – Study 014

The dose finding studies across the CZP RA development program are adequate. Study 014 supports the proposed alternative maintenance dose regimen of 400 mg q4w + MTX in patients with active RA. The primary efficacy results are consistent with efficacy of the 400 mg q4w + MTX regimen. The ACR response, however, were overall lower in Study014 than in the later studies 027 and 050 (**Tables 83** and **84**). For example, ACR20 responses in Study 014 were approximately 50% at Week 24 compared to approximately 60% in Study 027. Similarly, ACR50 responses were 18% in Study 014 versus 40% in Study 027 and ACR70 responses were not seen in CZP-treated patients in Study 014 but were seen in approximately 20% of patients in Study 027. These findings cannot be explained by a higher rate of immunogenicity in Study 014 since only 4% of patients developed anti-CZP antibodies. One potential explanation for the differences is the additional loading dose regimen in Study 027 and 050 consisting of 400 mg q2w for these doses.

Table 83. ACR Response Rates at Week 24 - Study 014 and Study 011

Study 014: ACR Response Rates at Week 24			
	PBO + MTX N = 119	CZP 400 mg q 4w + MTX N = 124	P-value
ACR 20 [a]	23%	46%	<0.001
ACR 50	6%	18%	≤ 0.01
ACR 70	2%	0%	ns
Study 011: ACR Response Rates at Week 24			
ACR 20 [a]	9%	46%	<0.001
ACR 50	4%	23%	<0.001
ACR 70	0%	6%	≤ 0.05

Table 84. ACR Response Rates at Week 24 - Study 027 and 050

Study 027: ACR Responses at Week 24				
	PBO + MTX n = 199	CZP 200 mg q2w + MTX N = 393	CZP 400 mg q2w + MTX N = 388	P-value
ACR 20 [(a.)]	14%	59%	61%	<0.001
ACR 50	8%	37%	40%	<0.001
ACR 70	3%	21%	21%	<0.001
Study 050: ACR Responses at Week 24				
	PBO + MTX N = 127	CZP 200 mg q 2w + MTX N = 246	CZP 400 mg q2w + MTX N = 245	P-value
ACR 20 [(a.)]	9%	57%	58%	<0.001
ACR 50	3%	33%	33%	<0.001
ACR 70	1%	16%	11%	<0.001

6.3.9 Discussion of Persistence of Efficacy and/or Tolerance Effects – Study 014

There was no evidence for the development of tolerance to CZP in Study 014.

6.3.10 Additional Efficacy Issues/Analyses – Study 014

There were no additional efficacy analyses for Study 014.

6.3.11 Summary of Efficacy –Study 014

Study 014 employed the lyophilized formulation of CIMZIA®. The study was global in the scope of clinical sites. The result of the primary efficacy analysis, the ACR20 response at Week 24 (mITT population), was statistically significant and clinically meaningful for CZP 400 mg q4w + MTX group with 56 patients (46%) compared to the PBO + MTX group with 27 patients (23%) ($p < 0.001$). The various sensitivity analyses supported the primary analysis results with a statistically significant difference with respect to ACR20 responder rate, favoring CZP 400 mg q4w + MTX over PBO + MTX.

Overall, though ACR20 and ACR50 responses in Study 014 were statistically significant, the magnitude of effect was less in Study 014 with CZP 400 mg q4w + MTX regimen compared to the ACR outcomes in Study 027 and 050 with CZP 200 mg and 400 mg q2w + MTX regimen. The ACR70 response at Week 24 in Study 014 was assessed in only 2 patients. Due to the small number of patients, this outcome was not considered clinically meaningful.

Overall, the individual components of the ACR composite score (tender/painful joint count, swollen joint count, patient's assessment of arthritis pain (VAS), patient and physician global assessment of arthritis, HAQ-DI, CRP, and ESR) all showed statistically significant improvement favoring CZP 400 mg q4w + MTX treatment group over the PBO + MTX treatment group at Week 24.

There were an insufficient number of patients (6, 5%) from which to assess ACR20 efficacy in the presence of anti-CZP antibody. Overall, the incidence of anti-CZP antibodies was not observed to be different between the two formulations, lyophilized versus the liquid formulation intended for the commercial market.

Overall, the proposed dose regimen of CZP 400 mg q4w + MTX achieved the primary efficacy endpoint, as measured by the ACR20 response at 24 weeks. The magnitude of this treatment effect for CZP 400 mg q4w + MTX was not as great in Study 014 compared with the ACR20 response at 24 Weeks in Study 027 and 050 with CZP 200 mg or 400 mg q2w + MTX. Studies 027 and 050 differ from Study 014 in providing an initial loading dose of CZP (400 mg at Weeks 0, 2 and 4). The primary efficacy analyses in Study 014 were supported by the various sensitivity analyses and by the components of the ACR response criteria.

6.4 Indication – Study 011

The proposed indication in Study 011 is the same as reported in Study 027, 050 and 014. Study 011 is the single monotherapy study in the CIMZIA® RA development program.

6.4.1 Methods – Study 011

The efficacy data contained in Section 6.4 of this review were generated from Study CDP870-011 (Study 011), a 24-week, randomized, double-blind, placebo-controlled study of CZP 400 mg q4w without background MTX therapy compared to PBO in patients who had failed at least one DMARD. This study was reviewed to assess the sponsor's efficacy submission. The analysis of the primary efficacy endpoint, the ACR response at Week 24, as well as the secondary and exploratory endpoints, was conducted for Study 011. All of the primary and secondary efficacy analyses were confirmed by the FDA's statistical reviewer, Katherine Meaker, PhD. The primary and secondary endpoints were discussed in the General Discussion of Endpoints section under Section 6.1. Also see Section 5.3 Discussion of Individual Studies.

6.4.2 Demographics – Study 011

The patient population was well balanced across the two treatment groups for demographic, Baseline characteristics, history of RA disease and extra-articular features of RA at Baseline. The mean age of patients was 54 years and the majority of patients were Caucasian (81%). See **Tables 85, 86,** and **87.** The number and proportion of patients with mild ($3.2 \geq DAS28 \leq 5.1$) disease activity was larger in the CZP 400 mg group, 17 (15%) patients compared to the PBO group with 6 (6%) patients. Overall, there were no clinically meaningful differences across the two treatment groups in the Baseline ACR components.

Table 85. Patient Demographics and Extra-Articular Features of RA - Study 011

Demographic Baseline Charactersitics, Extra-articular Features of RA - Study 011 (All randomized Patients)			
	PBO N = 109	CZP 400 mg sc q4w N = 111	Overall N = 220
Age (yrs)			
Mean (SD)	55 (12)	53 (13)	54 (12)
Gender			
Male	12 (11%)	24 (22%)	36 (16%)
Female	97 (89%)	87 (78%)	184 (84%)
Race			
Asian	1 (1%)	2 (2%)	3 (1%)
Afro-American	8 (7%)	13 (12%)	21 (10%)
Caucasian	87 (80%)	90 (81%)	177 (81%)
Not Listed	13 (12%)	6 (5%)	19 (9%)
Rheumatoid Nodules			
Yes	30 (28%)	29 (26%)	59 (27%)
No	79 (73%)	82 (74%)	161 (73%)
Keratoconjunctivitis Sicca			
Yes	14 (13%)	12 (11%)	26 (12%)
No	95 (87%)	99 (89%)	194 (88%)
Neuropathy			
Yes	3 (3%)	2 (2%)	5 (2%)
No	106 (97%)	109 (98%)	215 (98%)
Vasculitis			
Yes	1 (1%)	0	1 (1%)
No	108 (99%)	111 (100%)	219 (100%)

Revised from sponsor Table 11.1, page 104 and Table 11.3 page 107 of 5470

Table 86. History of RA - Study 011

Demographic Characteristics - Study 011 (ITT Population)		
Characteristics	PBO N = 109	CZP 400 mg sc q4w N = 111
Duration of Disease		
Mean (SD)	10 (10)	9 (8)
Median	7 (0.5, 47)	7 (0.4, 39)
Rheumatoid Factor		
Positive	109	110
Number of Prior DMARDs		
Median (range)	2 (1, 8)	2 (0, 7)
1 DMARD	49 (45%)	42 (38%)
2 DMARDs	27 (35%)	38 (34%)
3 DMARDs	20 (18%)	16 (14%)

Revised from sponsor Table 11.2, page 106 of 5470

Table 87. Disease Characteristics - Study 011

Baseline Values for ACR Characteristics - Study 011 (All randomized patients)			
	PBO N = 109	CZP 400 mg sc q4w N = 111	Overall N = 220
Duration of Morning Stiffness (hr)			
Mean (SD)	5 (7)	5 (7)	5 (7)
Median (range)	2 (0, 24)	2 (0, 24)	2 (0, 24)
C-Reactive Protein (CRP) mg/L			
Geometric Mean (95% CI)	11 (9, 15)	12 (10, 15)	12 (10, 14)
ESR (mm/hr)			
Geometric Mean (95% CI)	36 (31, 41)	31 (26, 37)	33 (30, 37)
Disease Activity Score [DSA28(3)]			
Mean (SD)	6 (1)	6 (10)	6 (1)
DAS Group			
≥ 3.2 to ≤ 5.1	6 (6%)	17 (15%)	23 (11%)
> 5.1	102 (94%)	94 (85%)	196 (89%)
Remission (DAS < 2.6)			
No	108 (99%)	111 (100%)	219 (99%)
Yes	1 (0%)	0	1 (0%)

Revised from sponsor Table 11:4, page 109 of 5470.

Disease Modifying Anti-inflammatory Drugs - Study 011

The pre-specified design of Study 011 required that patients discontinue DMARDS at least 28 days prior to enrollment. The most frequent concomitant medication was prednisone, taken by > 36% of patients in both treatment groups. See **Table 88.** There was no reported prior TNF-inhibitor therapy among the enrolled patients. Overall, there were no significant differences between the two groups with respect to concomitant medications.

Table 88. Past DMARDs for RA - Study 011

Past DMARDs for RA - Study 011 (All Randomized Population)	PBO N = 109	CZP 400 mg sc q4w N = 111
Corticosteroids		
Yes	64 (59%)	77 (70%)
No	45 (41%)	34 (31%)
NSAIDs/COX-2		
Yes	95 (87%)	93 (84%)
No	14 (13%)	18 (16%)
DMARDs		
Yes	109 (100%)	109 (100%)
No		
Other Arthritis Treatments		
Yes	5 (5%)	11 (10%)
No	104 (94%)	100 (90%)
Analgesics		
Yes	48 (44%)	49 (44%)
No	61 (56%)	62 (56%)

Revised sponsor Table 11:5, page 110 of 5470.

6.4.3 Patient Disposition – Study 011

A total of 220 patients were randomized in a ratio of 1:1 (across 36 centers in 3 countries) with 109 and 111 patients randomized to receive PBO and CZP 400 mg q4w, respectively. There were 138 (63%) of patients who completed Week 12 and 104 (47%) of patients who completed Week 24. See **Table 89.** Of the 109 patients in the PBO group, 50 (46%) completed through Week 12 and 28 (26%) completed through Week 24. Of the 111 patients who received CZP 400 mg, 88 (79%) completed through Week 12 and 76 (69%) completed through at Week 24.

A total of 116 (53%) patients withdrew from Study 011, of whom 81 (74%) received PBO and 35 (32%) received CZP 400 mg. The most frequent reasons for withdrawal were as follows: lack of efficacy in 3 (67%) and 24 (22%) of patients in PBO and CZP 400 mg, respectively; AEs in 5 (6%) and 5 (5%) of patients who received PBO and CZP 400 mg; and protocol violation(s) in 0 (0%) and 4 (4%) patients who received PBO and CZP 400 mg, respectively. A total of 81 (74%) and 89 (80%) of patients who received PBO and CZP 400 mg, respectively, were included in the per protocol sensitivity analysis.

Table 89. Summary of Patient Disposition – Study 011

Patient Disposition - Study 011 (All pts. randomized)			
	PBO N= 109 n (%)	CZP 400 q4w N=111 n (%)	Overall N=220 n(%)
Randomized but did not take CZP dose	0	0	0
Randomized	109	111	220
Completed at Week 12	50 (46%)	88 (79%)	138 (63%)
Completers who entered Study 015	28	75	
Completed at Week 24	28 (26%)	76 (69%)	104 (47%)
Withdrawals	81 (74%)	35 (32%)	116 (53%)
Discontinuation due to AEs	5* (6%)	5 (5%)	7 (3%)
Lack of efficacy	73* (67%)	24 (22%)	99 (45%)
Deaths	0	0	0
Protocol violations	0*	4 (4%)	5 (2%)
Lost to follow-up	3 (3%)	0	3 (1%)
Consent withdrawn	0	2 (2%)	2 (1%)
Pts. with non-mising data for the primary efficacy endpoint [a.]	93%	91%	92%

* Sponsor reported 81 (74%) withdrawals in the PBO-control arm. There are 3 additonal withdrawals; therefore, there are 84 (77%) withdrawals in the PBO-control. Discontinuation due to Aes in the PBO group is 5 (6%) not 2 (2%), lack of efficacy is 73 (67%) not 75 (69%) and protocol violation is 0 not 1 (1%).
Pt. # 1139 withdrawn due to AE (influenza like illness) not to lack of efficacy; Pt # 1160 withdrawn due to AEs (2 injection stie reactions) not to lack of efficacy. Pt. # 1172 withdrawn due to AE (atrial fibrillation) not protocol violation or consent withdrawn. These three patients were all PBO treated patients.
(a.) Patients with adequate data who completed or dropped out due to lack of efficacy. Therefore, the data are adequate to calculate the primary efficacy analysis for ACR20 response at Week 24. Patients who dropped out due to lack of efficacy or completed Study 011 were permitted to enter open-label Study 015.
Revised sponsor Table 10.2, page 98 of 5470.

Patient Withdrawals by Time and ACR Response Status – Study 011

Of the 116 patients withdrawn from Study 011, 104 (90%) were considered non-responders with respect to the primary efficacy endpoint, ACR20 response at Week 24: 81 and 35 patients received PBO and CZP 400 mg q4w, respectively. The largest number of patients withdrew between Week 8 and 12 (32 patients) and between Week 12 and 16 (47 patients). See **Table 89.** The pre-specified study design permitted patients to enter the OL Study 015 after completing 12 weeks of treatment in Study 011.

Proportion of Patients Randomized by Region and Country – Study 011

Study 011 was conducted in 36 centers in the following 3 countries: Austria (2 centers), Czech Republic (5), and the United States (29). The proportion of patients randomized by region and country is reported in **Table 90.** Overall, the number of enrolled patients across these 3 countries was well balanced.

Table 90. Proportion of Patients Randomized by Region and Country – Study 011

Proportion of Patients Randomized by Region and Country - Study 011			
Country	PBO N = 109	CZP 400 mg sc q4w N =111	Overall N = 220
USA	82	83	165
Czech Republic	25	27	52
Austria	2	1	3

Revised from sponsor Table 10.1, page 97 of 5470.

6.4.4 Analysis of Primary Endpoint(s) – Study 011

ACR Response – Study 011

Study 011 was a 24 week randomized, placebo-controlled trial designed to evaluate CZP 400 mg q4w monotherapy in patients with active RA without any DMARD background therapy. This study employed the lyophilized CIMZIA® formulation which is not intended for the commercial market. The primary efficacy analysis was the ACR20 response at Week 24 in the mITT population.

The monotherapy CZP 400 mg treatment group demonstrated statistically significant and clinically meaningful efficacy as measured by the ACR20 response at Week 24 with 50 (46%) of patients compared to the 10 (9%) of patients in the PBO group as ACR responders ($p<0.001$). See **Table 91.** Overall, this clinically meaningful outcome as measured by the primary endpoint ACR20 response at 24 weeks was consistent with the same primary endpoint outcome in Study 014, the only difference being the inclusion of MTX as background therapy in Study 014.

Sensitivity Analyses – Study 011

In support of the statistically significant outcome shown for the primary efficacy endpoint, ACR 20 response at 24 weeks, the pre-specified sensitivity analysis mITT demonstrated a favorable outcome for the primary endpoint: 15 (14%) and 54 (49%) of patients in the PBO group compared to the CZP 400 mg q4w group were ACR20 responders ($p<0.001$). The pre-specified sensitivity analyses based on excluding the protocol violators (mITT) and based on excluding CZP 400 mg q4w protocol violators (mITT) showed that the proportion of ACR20 responders was higher in the CZP group than in the PBO group, 47 (53%) compared with 8 (9%) ($p<0.001$) and 47 (53%) compared with 10 (9%), respectively ($p<0.001$). See **Table 92.**

An additional pre-specified responder analysis (mITT population) for the primary endpoint also showed consistent statistically significant outcomes for the primary ACR20 response favoring the CZP 400 mg q4w group with 48 (55%) of patient responders compared to the PBO group 7 (15%) patients responders ($p<0.001$).

When the pre-specified sensitivity analysis by LOCF approach was employed, statistical significance was shown favoring CZP 400 mg q4w over the PBO group at Week 1 ($p<0.001$) through Week 24 ($p<0.001$). At Week 24, 16 (15%) of the PBO group and 56 (51%) of the CZP 400 mg q4w group were ACR20 responders. Overall, the pre-specified sensitivity analysis supported the primary efficacy endpoint outcome. See **Figure 13.**

In addition, the pre-specified sensitivity analysis by the general estimating equation (GEE) methodology supported the primary efficacy endpoint outcome with a statistically significant difference favoring the CZP 400 mg q4w group with 56 (51%) of patients as ACR20 responders compared to the PBO group with 16 (15%) of patients as ACR20 responders (p<0.001).

Table 91. ACR20 Response at Week 24 – Study 011

ACR20 Response at Week 24 - Primary Analysis - Study 011 (mITT Population)			
	PBO N = 109	CZP 400 mg sc q4w N = 111	p-Value [a.]
Responder [b.]	10 (9%)	50 (46%)	<0.001

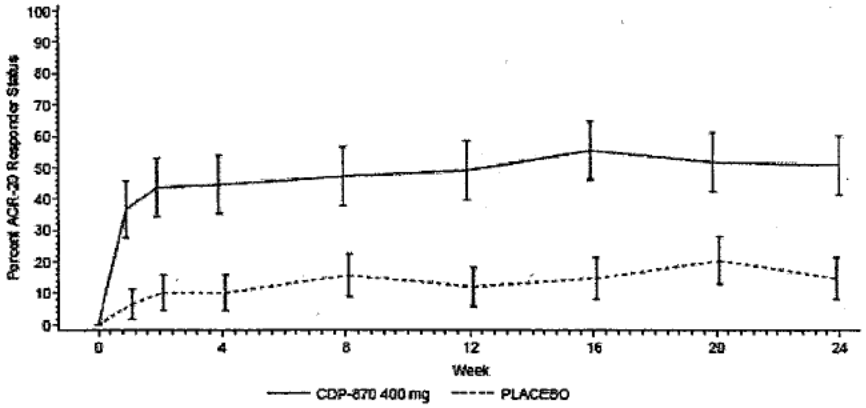
(a.) Cochran-Mantel-Haenszel (CMH) test of treatment comparison stratified by country.
(b.) A patient was considered a responder if he/she met the criteria of ACR20 improvement over Baseline at Week 24. Any patient who withdraws from the study at any time for any reason was considered a non-responder. Revised from sponsor Table 14.2.1:1, page 428 of 5470.

Table 92. ACR20 Response at Week 24 – Study 011

ACR20 Response at Week 24 - Sensitivity Analyses - Study 011 (mITT Population)			
	PBO N = 109	CZP 400 mg q4w N = 111	p-Value [a.]
Modified Intent-to-Treat (mITT)			
Responder [b.]	15 (14%)	54 (49%)	<0.001
Excluding Protocol Violators (mITT)			
Responder [b.]	8 (10%)	47 (53%)	<0.001
Excluding CZP Treated Protocol Violators			
Responder [b.]	10 (9%)	47 (53%)	<0.001

(a.) Cochran-Mantel Haenszel test of treatment comparison stratified by country.
(b.) A patient was considered a responder if he/she met the criteria of ACR20 improvement over Baseline at Week 24. Any patient who withdraws from the study for any reason at any time was considered a non-responder.
Revised from sponsor Table 14.2.1:2 through Table 14.2.1:4, pages 429 to 431 of 5470.

Figure 13. ACR20 Response (LOCF) Percent Response Over Time by Rx Group – Study 011



Note: The week 0 response was not carried forward, therefore n= 106 (PBO) and 109 (CZP 400 mg q4w), at all other weeks n = 108 and 110, respectively.

ACR20 Response by Antibody Status – Study 011

Overall, throughout Study 011, a total of 25 (23%) patients developed detectable anti-CZP antibody (> 2.4 Units/mL). At 24 weeks, 19 patients (18%) were anti-CZP antibody positive and 89 (82%) were anti-CZP antibody-negative. An analysis by LOCF at Week 24 showed 8 (33%) anti-CZP antibody positive patients were ACR20 responders which is lower than the overall ACR20 response rate in the CZP-treated group (**Table 93).** In contrast, in Study 027, in which CZP was given in combination with background MTX, 11% of patients in the CZP 200 mg q2w + MTX group and 2% of patients in the CZP 400 mg q2w + MTX group developed anti-CZP antibodies. These data suggest that CZP monotherapy is associated with a higher rate of immunogenicity and patients developing anti-CZP antibodies have an increased risk for decreased ACR response compared to anti-CZP antibody negative patients.

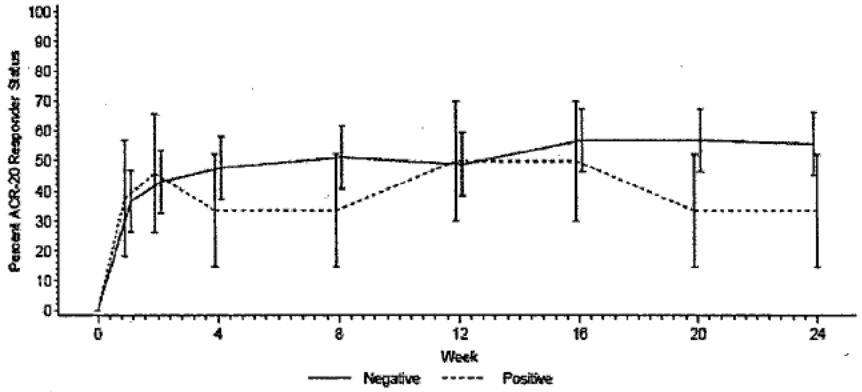
Figure 14 shows a plot of the ACR-20 Response (LOCF) by anti-CZP antibody status. There was no observed difference between responders and non-responders with respect to plasma CZP concentrations at any time point.

Table 93. ACR20/50/70 Response by Anti-CZP Antibody Status (LOCF) – Study 011
(LOCF) Revised from sponsor Table 14.2.15:5, page 591 of 5470

ACR20 Response by Anti-CZP Antibody Status - Study 011 (All randomized patients)		
CZP 400 mg sc q4w (N = 111)		
	CZP Antibody Negative	CZP Antibody Positive
	≤ 2.4 U/mL [a.] N = 86	> 2.4 U/mL [a.] N = 25
ACR 20 Response		
Week 12 LOCF Responder [b.]	42 (49%)	12 (50%)
Week 24 LOCF Responder [b.]	48 (56%)	8 (33%)
ACR 50 Response		
Week 12 LOCF Responder [b.]	17 (20%)	4 (17%)
Week 24 LOCF Responder [b.]	22 (26%)	4 (17%)
ACR 70 Response		
Week 12 LOCF Responder [b.]	4 (5%)	1 (4%)
Week 24 LOCF Responder [b.]	5 (6%)	1 (4%)

(a.) Based on maximum antibody level during 24 weeks of treatment.
(b.) Responder: at least 20/ 50/70% improvement from baseline in the number of tender /painful joints and in the number of swollen joints, as well as at least 20/50/70% improvement from Baseline in at least 3 of the following 5 assessments: physician global, patients global, patient's assessment of arthritis pain, CRP, or mHAQ-DI.
(c.) CMH test of antibody comparison stratified by country.
Revised from sponsor Tables 14.2.15:5 to 7, pages 591 to 593 of 5470.

Figure 14. ACR20 Response (LOCF) by Anti-CZP Antibody Status
Sponsor figure 14.2.1:2, page 456 of 5470)



Data Source: Tables 14.3.9:1 (Incidence of Anti-CDP-870 Antibody Formation), Table 14.2.1:15 (ACR-20 Response by Week), Listings 16.2.6.13 (ACR Improvement in Disease Activity) and 16.2.5.3 (CDP870 Plasma Concentration and Anti-CDP870 Antibody Levels).
Note: Week 0 response was not carried forward, therefore at Week 0 n=106 for Placebo and n=109 for CDP870. At all other visits n=108 for placebo and n=110 for active.
SAS Program: F_ACR202.SAS

6.4.5 Analysis of Secondary Endpoints – Study 011

ACR50 Responses at Week 24 – Study 011

The ACR50 response at 24 weeks showed statistical significance favoring the CZP 400 mg q4w group over the PBO group, 4 (4%) compared to 25 (23%) of patients (p<0.001). See **Table 94.**

Table 94. ACR50 Response at Week 24 – Study 011

ACR50 at Week 24: Sensitivy Analyses			
ACR50 at Week 24: Sensitivity Analysis - Modified ITT			
	PBO N = 109	CZP 400 mg N = 111	P-value
Responder [a.]	5 (5%)	26 (24%)	<0.001
Excluding Protocol Violators (mITT)			
Responder [a.]	3 (4%)	23 (26%)	<0.001
Excluding CZP Treated Protocol Violators			
Responder [a.]	4 (4%)	23 (26%)	< 0.001

Revised from sponsor Tables 11:12, 14.2.2:2 and 14.2.2:3, page 118 and pages 459 – 460 of 5470.

ACR70 Response at Week 24 – Study 011

Only 6 (6%) patients in Study 011 showed an ACR70 response and all of these patients were treated with CZP 400 mg sc q4w, thereby showing a statistically significant outcome for the active treatment group (p = 0.013). See **Table 95.** These data should be interpreted with caution due to the very small number of patients.

Table 95. ACR70 Response at Week 24 – Study 011

ACR70 Response at Week 24 - Study 011 (mITT population)			
Week 24	PBO N = 109	CZP 400 mg q4w N = 111	p-value
Responder [a.]	0	6 (6%)	0.013

(a.) a patient was consided a responder if he/she met the criteria of ACR70 improvement over Baseline at Week 24. A patient who withdraws from the study at any time during the study for any reason was considered a non-responder.
Revised from sponsor Table 14.2.3:2 through 4, pages 488 to 490 of 5470.

Individual ACR Components – Study 011

To determine whether the results in the composite ACR index were broad or were limited to a subset of the ACR components, we examined the outcomes of the individual components of the ACR composite score (**Table 96**). CZP-treated patients from Study 011 showed significantly higher improvement compared to PBO as measured by each of the 7 individual core ACR response index components ($p<0.001$) with the exception of the ESR ($p=0.05$ at Week 20).

Table 96. ACR Components – Mean Change Analysis in Study 011 (mITT population)

ACR Components - Mean Change Analysis - Study 011 (mITT)			
	PBO N=109	CZP 400 mg q4w N=111	p-value
Tender/Painful Joint Count			
Baseline Mean (SD)	28 (13)	30 (14)	
Week 24, Mean (SD)	24 (15)	16 (16)	
Week 1, LS Mean Change [(a.)]	-4.6	-9.8	
Week 24, LS Mean Change [(a.)]	-7.3	-16	<0.001
Swollen Joint Count			
Baseline Mean (SD)	20 (9)	21 (10)	
Week 24, Mean (SD)	16 (13)	12 (11)	
Week 1, LS Mean Change [(a.)]	-2.8	-6.0	
Week 24, LS Mean Change [(a.)]	-6.3	-11.6	<0.001
Patient's Global Assessment of Arthritis			
Baseline Mean (SD)	3.3 (0.8)	3.3 (0.8)	
Week 24, Mean (SD)	3.4 (1)	2.7 (1)	
Week 1, LS Mean Change [(a.)]	-0.1	-0.5	
Week 24, LS Mean Change [(a.)]	0.0	-0.7	<0.001
Physician's Assessment of Arthritis			
Baseline Mean (SD)	3.6 (0.6)	3.6 (0.7)	
Week 24, Mean (SD)	3.4 (1)	2.6 (1)	
Week 1, LS Mean Change [(a.)]	-0.1	-0.7	
Week 24, LS Mean Change [(a.)]	-0.2	-1.1	<0.001
Patient's Assessment of Arthritis Pain (VAS)			
Baseline Mean (SD)	54.8 (21)	58 (22)	
Week 24, Mean (SD)	60 (27)	39 (30)	
Week 1, LS Mean Change [(a.)]	-5.2	-16.7	
Week 24, LS Mean Change [(a.)]	1.7	-21	<0.001
Health Assessment Questionnaire - Disability Index (HAQ-DI)			
Baseline Mean (SD)	1.6 (0.7)	1.4 (0.7)	
Week 24, Mean (SD)	1.6 (0.7)	1.04 (0.70)	
Week 1, LS Mean Change [(a.)]	0.04	-0.23	
Week 24, LS Mean Change [(a.)]	0.13	-0.36	<0.001
C-Reactive Protein (CRP)			
Baseline Geo. Mean [95%CI]	11.3 [9-15]	11.6 [9-15]	
Week 24, Geo. Mean [95%CI]	13.5 [10-18]	6.4 [5-9]	
Week 1, LS Mean Change [(a.)]	1.1	0.3	
Week 24, LS Mean Change [(a.)]	1.2	0.6	<0.001
Erythrocyte Sedimentation Rate (ESR)			
Baseline GEO. Mean [95%CI]	36 [31-41]	31 [26-37]	
Week 24, Geo. Mean [95%CI]	34 [29-40]	25 [20-30]	
Week 1, LS Mean Change [(a.)]	1	0.7	
Week 24, LS Mean Change [(a.)]	0.9	0.8	0.005 (at wk 20)

6.4.6 Other Endpoints – Study 011

6.4.7 Subpopulations – Study 011

There were no significant findings for the subpopulations in this supportive study.

6.4.8 Analysis of Clinical Information Relevant to Dosing Recommendations – Study 011

The dose-finding trials across the CZP RA development program were adequate. Study 011 employed the lyophilized CIMZIA® formulation which is not the commercially intended formulation. Study 011 supported the efficacy of CZP 400 mg q4w monotherapy dose regimen in patients with active RA. The analysis of the primary efficacy endpoint, ACR20 response at 24 weeks in the mITT population, showed that the CZP 400 mg q4w monotherapy was statistically significant and clinically meaningful compared to the PBO treatment group and supported the primary endpoint results as shown in Study 027, 050 and 014. There was a decreased treatment effect with CZP 400 mg q4w, as measured by the secondary efficacy endpoints, ACR50 and ACR70 responses at 24 weeks, in contrast to the treatment effect with the same secondary endpoint as shown in Study 027 and 050 with CZP 200 mg and CZP 400 mg q2w + MTX dose regimen.

Although the treatment effect was not as robust as with the q2w dose regimen which included background MTX, the monotherapy dose regimen showed a clinically meaningful response to the primary endpoint. Therefore, the proposed alternative dose of CZP 400 mg every 4 weeks is acceptable maintenance therapy in patients with active RA without background DMARD therapy.

6.4.9 Discussion of Persistence of Efficacy and/or Tolerance Effects – Study 011

The CZP 400 mg q4w dose regimen achieved an ACR20 response at Week 24 showing the persistence of efficacy over time. This outcome in Study 011 supports the co-primary efficacy endpoint as measured by the ACR20 response in Study 027, and the same endpoint as the primary efficacy endpoint in Study 050 and 014 at 24 weeks. There was a trend toward loss of the treatment effect of CZP administered as monotherapy in Study 011 as shown by the decreased ACR50 and ACR70 responses at week 24 compared with the 200 mg and 400 mg every two week dose regimens.

6.4.10 Additional Efficacy Issues/Analyses – Study 011

All efficacy analyses are included in the appropriate subsections of Section 6.0 Review of Efficacy.

6.4.11 Summary of Efficacy

Study 011 employed the lyophilized CIMZIA® formulation which is not the commercially intended formulation and was a multinational trial. The result of the primary efficacy analysis, ACR20 response at 24 weeks in the mITT population, was statistically significant and clinically meaningful for CZP 400 mg q4w monotherapy as the proposed alternative maintenance dose regimen for the treatment of the signs and symptoms of active RA.

By Week 24, 9% of patients in the PBO group compared to 46% of patients in the CZP 400 mg q4w group were ACR20 responders ($p<0.001$). This result was supported by the pre-specified sensitivity analyses for the ACR20 outcomes.

The secondary efficacy endpoint, the ACR50 response at 24 weeks in the MITT population, supported the primary endpoint. The secondary efficacy endpoint, the ACR50 response at Week 24 in the mITT population, showed 23% and 4% of patients in the CZP 400 mg q4w and PBO treatment group, respectively ($p<0.001$). A total of 6% of CZP 400 mg q4w treated patients (6 of 111) showed an ACR70 response compared to none of the PBO-treated patients ($p = 0.013$). The number of patients who achieved an ACR70 response was small and, therefore, these data should be interpreted with caution.

In contrast, both Study 027 and 050 showed a larger treatment effect for the ACR70 response: CZP 200 mg q2w + MTX, CZP 400 mg q2w + MTX, lyophilized formulation in Study 027 and the liquid formulation in Study 050. For example, approximately 20% of patients receiving CZP in Study 027 had an ACR70 response compared to 3% of controls.

Overall, the CZP 400 mg q4w monotherapy regimen showed meaningful treatment effect with the Tender Painful Joint Count, Swollen Joint Count, Physician Global Assessments of Arthritis, HAQ-DI, CRP and ESR. The single exception among the individual components of the ACR was with the Patient's Global Assessment of Arthritis and its pre-specified categorical change analysis for this endpoint which failed to show any statistically significant differences between the two treatment groups, although the pre-specified sensitivity analysis based on repeated measures for the same endpoint showed statistically significant changes favoring CZP 400 mg over PBO from Week 1 ($p< 0.001$) through only Week 20 ($p< 0.001$).

Overall, CZP 400 mg q4w monotherapy without background DMARD therapy showed adequate and clinically meaningful outcomes based on the primary efficacy endpoint as measured by the ACR20 response at 24 weeks and the ACR50 response at 24 weeks among a variety of other endpoints. As consistently observed in the three other Phase 3 studies in the CZP RA program, the anti-CZP antibody positive patients tended to have less treatment effect as measured by the ACR20 response at 24 weeks compared with anti-CZP antibody negative patients.

In conclusion, the proposed CZP 400 mg q4w monotherapy regimen is effective in the treatment of signs and symptoms of patients with active RA but may be less effective than other regimens, particularly, those with background MTX. The product labeling for CIMZIA® in RA patients should show comparison of the ACR20, 50 and 70 efficacy results to adequately inform prescribing physicians of the treatment effect differences among CZP q4w monotherapy regimen, CZP q4w with MTX regimen, compared with CZP 200 mg and CZP 400 mg q2w with MTX as fixed dose regimens. The sponsor did not study CZP 200 mg q4w without background MTX or CZP 400 mg q4w monotherapy with a loading dose regimen in this submission.

6.5 Indication – Substudy 051

Prefilled Syringe (PFS) Self-Injection Assessment – Substudy 051

6.5.1 Methods – Substudy 051

See Section 5.3 Discussion of Individual Studies, Substudy 051

6.5.2 Demographics – Substudy 051

The demographics for Substudy 051 (**Table 97**) included all patients who agreed to participate in the self-injection administration and who completed at least one self-injection visit and one SIAQ© Post Self-Injection assessment. Out of 98 patients entering this Substudy, Amendment #2, only 1 patient failed to complete at least one self-injection. The reason for this failure was due to inability of the patient to administer the investigational product. Therefore, 97 patients were included in the SIAQ population: 10 patients in the USA, 30 in the Czech Republic and 57 in Poland. The characteristics of this population were representative of RA patients and those enrolled in the CZP RA studies.

Table 97 Demographic Characteristics of the SIAQ© Population at Baseline of the Feeder Study 051 – SIAQ© Population (Revised from sponsor Table 5:1, page 13 of 162)

Demographic Characteristics of the SIAQ Population at Baseline (Feeder Study 051, Open Label Long Term)	
Parameters	**All Patients (N = 97)**
Age (years), Mean, Range	52 yrs (28 - 69)
Gender (female), N (%)	74 (76%)
Body Mass Index (kg/m^2), Mean	27.5 (5)
Race (Caucasian(, N (%)	96 (99%)

6.5.3 Patient Disposition – Substudy 051

As demonstrated in **Table 98**, 97 patients performed at least one self-injection and completed the SIAQ© Post Self-Injection assessment and 90 (93%) patients completed all three consecutive self-injection visits.

Table 98. Patient Disposition - Substudy 051

Patient Disposition, PFS Substudy 051		
	# Pts. in SIAQ© Population	# Pts. able to perform 3 consecutive self-injections
All	97	90 (93%)
Dropouts/Withdrawals	7	
Missed a visit	5	
"Too painful on thumb"	1	
"Too tired"	1	

6.5.4 Analysis of Primary Endpoint(s) – Substudy 051

There was no formal statistical testing completed for Substudy 051. The percentages of patients reporting feeling very or extremely confident with their ability to safety self-inject demonstrated an increasing trend over consecutive visits (3 consecutive visits).

Ease of Handling and Administration with the PFS Self-Injection:

- Device Cap: At the first visit, more than 85% of patients agreed or strongly agreed that the cap was easy to remove, that it fit comfortably in their hands and that the instrument was easy to use. Only one patient (1%) strongly disagreed with one statement, namely that the cap was easy to remove.
- PFS Plunger: A large majority of patients were in agreement or strong agreement that they could easily depress the PFS plunger (84.5%) and they could administer the injection without any help (79.4%).
- Less then 8% of patients disagreed or strongly disagreed with any of these statements: 1 to 6 patients (1% to 6%) disagreed with any statement.

The majority of patients were moderately, very or extremely confident with their ability to safely self-inject (i.e., 79% at visit 1; 81% at visit 2; 81% at visit 3) and with their ability to self-inject in a clean and sterile way (i.e., 77% at visit 1; 84% at visit 2; 83% at visit 3). By the first visit, a majority of patients were confident (moderately, very or extremely) with their ability to inject in the right way (72.2%).

Overall, the percentages of patients reporting feeling moderately, very or extremely confident with their ability to safely self-inject increased from Visit 1 to Visit 3. Patients reported feeling not at all or a little confident with their ability to inject in the correct way remained similar across the 3 consecutive visits. The majority of patients willing to perform self-injection successfully self-injected CZP and showed easy handling of the instrument and administration of the study drug. Therefore, it appears from this small Substudy 051 employing the PFS and the SIAQ© assessment, that patients with RA willing to perform self-injections appear confident with their ability to self-inject CZP with the proposed PFS single use instrument and that it is safe to use as directed.

6.5.5 Other Endpoints – Substudy 051

There were no other parameters assessed in Substudy 051.

6.5.6 Subpopulations – Substudy 051

This section was not applicable to Substudy 051.

6.5.7 Analysis of clinical Information Relevant to Dosing Recommendations – Substudy 051

This section was not applicable to Substudy 051.

6.5.8 Discussion of Persistence of Efficacy and/or Tolerance Effects – Substudy 051

This section was not applicable to Substudy 051.

6.5.9 Additional Efficacy Issues/Analyses – Substudy 051

This section was not applicable to Substudy 051.

6.5.10 Summary of Efficacy – Substudy 051

In summary, in Substudy 051 which employed the PFS and the SIAQ© assessment, RA patients willing to perform self-injections appear confident with their ability to self- inject CZP with the proposed PFS. It was shown to be safe as directed. Assessment of the extractable volume after weighing the ejected solution was evaluated. Analyses to assess delivery of the proposed product intended amount from the PFS was not assessed. See the CMC review by Gurpreet Gill-Shanga, PhD and Barbara Rellahan, PhD.

7 Review of Safety

Summary of Safety

The total exposure to CZP in the RA population was adequate for the assessment of safety and tolerability of CZP in patients with active RA. The safety database in the pooled RA population studies included data for 2367 patients participating in 10 studies who received CZP (at any dose) and 647 patients who received PBO control. In these studies, CZP was tested with and without concomitant MTX. The dosing regimens in the Phase 3 program included CZP 200 mg and 400 mg given q2w with MTX and CZP 400 mg q4w with and without MTX. A loading dose (CZP 400 mg at Week 0, 2 and 4) was employed in Studies 027 and 050. No loading dose was employed in Studies 014 and 011 (monotherapy). The 120-Day Safety Update (120-DSU) database (submitted April 3, 2008) was also included in this safety review.

The most common treatment emergent adverse events (TEAEs) in CZP-treated patients were in the High Level Term (HLT) Infections and Infestations such as upper and lower respiratory tract infections and herpes viral infections, followed by musculoskeletal and connective tissue disorders, rashes, and hypertensive disorders. Overall, long-term CZP exposure through 24 months, compared with PBO-controlled studies, did not show an increased rate of TEAEs. In addition, no increase in the overall incidence of infections was observed with concomitant MTX. These results support the proposed labeling for CZP to be administered either in combination with MTX or alone.

The overall mortality rate in the CZP studies was comparable to the expected mortality rate in similar RA populations not receiving CZP. The causes of death (10 deaths in PBO-controlled studies and 23 deaths in extensions studies; and 2 additional deaths in the 120-DSU safety data from 15Jul2007 through 30Nov2007) were similar to what is reported with other RA patient populations treated with biologics [1].

In the PBO-controlled studies, the incidence of SAEs was higher (10%, 11% and 12% versus 7%) in CZP 200 mg and 400 mg q2w and CZP 400 mg q4w treatment groups versus the PBO-

control. The most common SAEs were Infections and Infestations and the most frequent were tuberculosis. Over all the countries in CZP studies, the total number of expected TB cases within a general population was 2.6, while the observed number of TB cases was 35 (14 confirmed), equivalent to a Standardized Incidence Ratio (SIR) of 13.7 [95% CI: 9.5-19.0] overall and SIR of 5.5 [95% CI: 3.0-9.1] for confirmed cases only. The incidence rate of TB in CZP RA studies is consistent with the Class of TNF blocking agents, especially considering the higher number of CZP study patients enrolled in countries with high incidences of TB. It is note worthy that the risk of TB did not increase with increased CZP exposure.

A total of 21 malignancy cases (excluding non-melanoma of skin) occurred in 21 patients during the CZP RA studies. All of these cases were in CZP treated patients. The incidence of malignancies (in CZP RA studies) was estimated as 6.41 per 100 pt-yrs compared to the expected rate of malignancies in the general population of 6.07 per 100 pt-yrs. The types and incidence of malignancies observed in the CZP RA studies were consistent with those reported in the general population with RA and similar to those seen with other TNF-blocking agents.[2] Lymphoma was observed in 3 patients in CZP RA studies with a SIR of 4.97 [95% CI: 1.03-14.54]. The calculated incidence rate for lymphoma in CZP (0.09 per 100 pt-yrs) was similar to other TNF inhibitors.

There was no evidence of a cardiac safety signal in CZP treated patients in the PBO-controlled or OL studies in this safety database. A higher incidence of auto-antibodies was observed in CZP treated patients versus PBO-control patients. A small number of patients with auto-antibodies developed a lupus-like syndrome or rash. Overall, these events are consistent with what has been observed with other TNF blocking agents.

The incidence of anti-CZP antibody formation was low (7%) overall in the PBO-controlled studies. CZP antibody positivity was more frequent (22%) with CZP monotherapy than with MTX combination (4%). The presence of anti-CZP antibody was not associated with an increase in AEs.

Bleeding events did not demonstrate increased risk when corrected for exposure adjusted data, PBO compared to All CZP Doses group. There was no observed increased rate in the open label (OL) studies.

In conclusion, CZP was generally well tolerated. The most common TEAEs were those seen commonly in the general RA population. There was no increase in all-cause mortality associated with CZP treatment. There was an increased risk of serious infections, specifically tuberculosis, associated with CZP treatment. The types and incidence of malignancies observed during the CZP RA trials were similar to those reported in general RA population. On careful inspection of this safety database, no cardiovascular signal was observed in the PBO-controlled and OL studies. Noteworthy, no apparent risk of increased CHF with long term exposure was observed. The current CIMZIA® labeling reflects the worsening of congestive heart failure (CHF) and the new onset CHF as well as increased mortality due to CHF reported with other TNF inhibitors.

References:
1. Jacobsson LTH, Turesson C, Nilsson J-A, et al. Treatment with TNF blockers and mortality risk in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007; 66:670-675.
2. Setoguchi S, Solomon DH, Weinblatt M, et al. tumor necrosis factor anatagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum 2006; 54(9):2757-2764.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The safety review was based on the data from the PBO-controlled RA trials [Study 002 (Phase 1), 004 (Panel 1), 011, 014, 027 and 050]. As the safety results in all the CZP studies were similar, these data were pooled. The pooled safety database for CZP in RA included data for 2,367 patients who received at least 1 dose of CZP and 647 who received at least one dose of PBO control. The clinical data cut-off was January 31, 2007 and the ongoing OL extension CZP RA studies safety cut-off was July 15, 2007. For purposes of analysis, the deaths reported in the Phase 2 dose-finding trials (Study 002 and 004) were not included in the final analysis of PBO-controlled trial deaths as these two trials employed CZP doses much higher than those employed in the four Phase 3 trials (027, 050, 014 and 011) which support for the proposed indication in patients with active RA. The review of safety data analyzed by dose revealed a consistent trend with slightly higher rate of AEs with 400 mg q4w compared to CZP 200 mg and 400 mg q2w dose regimen. It appears that this slightly higher rate was a reflection of trial population (011). The observed trend does not appear to be a concern.

The safety data reviewed was for 3 separate populations in the CZP RA program as shown in **Safety Table s1.** Population 1 included all patients in the pooled RA Population ("All Studies") safety database and in the source tables used in this review. Population 2 included the studies with concomitant MTX and Population 3 included studies without concomitant MTX. The OL studies in the CZP RA development program, the background MTX studies and those studies without background MTX, contain data according to the feeder study protocol.

Table s1. Controlled Studies in the RA Population (sponsor Table 2.7.4:5, 343 of 973)

Pooling Studies	Total N per Group in Pool				
	Placebo	CZP 200 mg every 2 weeks	CZP 400 mg every 2 weeks	CZP 400 mg every 4 weeks	All CZP doses
All Studies	(N=647)	(N=640)	(N=635)	(N=278)	(N=1774)
CDP870-002 (Phase 1)	12	-	-	-	24
CDP870-004 (Panel 1)	83	-	-	43	240
CDP870-011	109	-	-	111	111
CDP870-014	119	-	-	124	124
CDP870-027	199	392	389	-	781
CDP870-050	125	248	246	-	494
MTX Studies	(N=443)	(N=640)	(N=635)	(N=124)	(N=1399)
CDP870-014	119	-	-	124	124
CDP870-027	199	392	389	-	781
CDP870-050	125	248	246	-	494
Non-MTX Studies	(N=204)	-	-	(N=154)	(N=375)
CDP870-002 (Phase 1)	12	-	-	-	24
CDP870-004 (Panel 1)	83	-	-	43	240
CDP870-011	109	-	-	111	111

Note: CZP = certolizumab pegol; "-" = Not applicable.

7.1.2 Adequacy of Data

The quantity and quality of data were adequate with the exception of data for 25 patients from Site # 093 in Study 027/ OL Study 028 (10 patients) and from Site #104 in Study 050/ OL Study 051 (15 patients). Data for these 25 patients were removed from the pooled RA safety analyses after the database was locked because of violations of Good Clinical Practices and fraud.

Bioequivalence between the two investigational formulations (liquid vs lyophilized) was assumed because the data were similar. The safety data was not adjusted for the two investigational formulations. There were an adequate number of patients exposed for at least 12 months across the proposed CZP dose regimens. See discussion in Section 7.2.1 below.

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

The safety data were pooled across PBO-controlled CZP RA studies.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations in the CZP Clinical Development Program

Adequate exposure data across all of the proposed CZP dose regimens (e.g., CZP 200 mg and 400 mg q2w with background MTX, CZP 400 mg q4w with background MTX and 400 mg q4w without background MTX) were submitted to adequately assess the long-term safety.

There were 2,367 patients [3,218 patient-years (pt-yrs)] exposed across the OL and PBO-controlled CZP RA trials (All Studies) and 1,774 patients (957 pt-yrs) exposed across the PBO-controlled CZP RA studies. In the All CZP Doses group, there was more than 3-fold longer duration of exposure that in the PBO group (957 vs 225 pt-yrs). At least 70% of all CZP treated patients showed at least 12 months of exposure. See **Tables s2 and s3.** These data were consistent with the ICH E1 document which recommends that a safety database for a chronic disease indication include at least 1500 patients treated for any period of time, at least 300 patients treated for at least 6 months and at least 100 patients treated for at least 12 months. It is also consistent with the Division's usual recommendation for safety data on 1000-1500 patients treated for one year for immunosuppressive products for RA.

With the OL studies included, the submission contained data on at least 100 patients treated for at least 12 months for all the proposed CZP dose regimens. There were no OL data for CZP 200 mg q2w + MTX dose regimen as all patients who entered into an OL trial received CZP 400 mg q2w + MTX.

Table s2. Extent of Exposure: All Doses in All Studies in RA – Safety Population

Extent of Exposure - All CZP Doses (OL and PBO-Controlled studies) in RA					
	PBO N=647	CZP 200 mg q2w N=640	CZP 400 mg q2w N=1487	CZP 400 mg q4w N=513	All CZP Doses N=2367
Duration of Expos. (days)					
Mean (SD)	127 (73)	226 (117)	357 (162)	794 (514)	497 (324)
Min, Max	14, 366	14, 369	14, 714	28, 1543	14, 1543
Total Exposure (Pt.-Yrs.)	225	396	1453	1116	3,218
Duration of Exposure					
< 3 months	179 (28%)	35 (6%)	61 (4%)	67 (13%)	163 (7%)
≥ 3 to < 6 months	418 (65%)	342 (53%)	124 (8%)	28 (6%)	174 (7%)
≥ 6 to < 12 months	8 (1%)	12 (2%)	577 (39)	65 (13%)	367 (16%)
≥ 12 to < 18 months	42 (7%)	251 (39%)	478 (32%)	46 (9%)	846 (36%)
≥ 18 to < 24 months	0	0	247 (17%)	25 (5%)	535 (23%)
≥ 24 months	0	0	0	282 (55%)	282 (12%)
≥ 12	42 (7%)	251 (39%)	725 (49%)	353 (69%)	1663 (71%)

Revised from Sponsor Table 2.7.4:10, page 352 of 973

Table s3. Exposure in PBO-Controlled CZP RA Trials

Exposure in PBO-Controlled CZP RA Studies					
	PBO N=647	CZP 200 mg q2w N=640	CZP 400 mg q2w N=635	CZP 400 mg q4w N=278	All CZP Doses N=1774
Duration of Exposure (days)					
Mean (SD)	127 (73)	226 (117)	236 (116)	140 (41)	197 (115)
Median	112	168	168	167	168
Min, Max	14, 366	14, 369	14, 368	28, 217	14, 369
Total Expos. (pt.-yrs.)	225	396	410	106	957

Revised from sponsor Table 2.7.4:9, page 351 of 973

Patient exposure was subdivided into those treated with and without background MTX. These data showed more than a 3-fold higher exposure in patients with background MTX than in patients without background MTX [2,471.8 vs 746.2 pt-yrs in the All CZP Doses group]. See **Tables s4** and **s5.**

Table s4. Exposure with Concomitant Methotrexate in CZP Trials – Safety Population

Extent of Exposure - Concomitant Methotrexate Studies - Safety Population					
	PBO + MTX N = 443	CZP 200 mg q2w + MTX N = 640	CZP 400 mg q2w + MTX N = 1487	CZP 400 mg q4w + MTX N = 228	All CZP Doses N = 1814
Duration of Expsoure in (days)					
Mean (SD)	144 (78)	226 (117)	357 162)	989 (481)	498 (297)
(Min., Max)	14, 366	14, 369	14, 714	28, 1543	14, 1543
Total Exposure (yrs)	175	396	1453	618	2472
Duration of Exposure					
< 3 months	31 (7%)	35 (6%)	61 (4%)	11 (5%)	103 (6%)
≥ 3 to < 6 months	366 (83%)	342 (54%)	124 (8%)	9 (4%)	94 (5%)
≥ 6 to < 12 months	4 (1%)	12 (2%)	577 (39%)	13 (8%)	227 (13%)
≥ 12 to < 18 months	42 (10%)	251 (39%)	478 (32%)	28 (12%)	746 (41%)
≥ 18 to < 24 months	0	0	247 (17%)	14 (6%)	491 (27%)
≥ 24 months	0	0	0	153 (67%)	153 (8%)
≥ 12 months	42 (10%)	251 (39%)	725 (49%)	195 (85%)	1390 (76%)
Revised from sponsor Table 7.2:1 and 3, page 22 and 33, respectively, of 48					

Revised from sponsor Table 7.2:1 and 3, pages 22 and 33, respectively, of 48

Table s5. Exposure without Concomitant Methotrexate in CZP Trials – Safety Population

Extent of Exposure: Non-Methotrexate Studies - Safety Population			
	Placebo N =204	CZP 400 mg q4w N = 285	All CZP Doses N = 553
Duration of Exposure (days)			
Mean (SD)	89 (43)	639 (487)	492 (398)
Min, Max	28, 196	28, 1344	28, 1344
Total Exposure (years)	50	499	746
Duration of Exposure			
< 3 months	148 (73%)	56 (20%)	60 (10%)
≥ 3 to < 6 months	52 (26%)	19 (7%)	80 (15%)
≥ 6 to < 12 months	4 (2%)	52 (18%)	140 (25%)
≥ 12 to < 18 months	0	18 (6%)	100 (18%)
≥ 18 to < 24 months	0	11 (4%)	44 (8%)
≥ 24 months	0	129 (45%)	129 (23%)
≥ 12	0	158 (55%	273 (49%)
Revised from sponsor Tables 7.3:2-3, pages 38 and 48 of 48.			

Two different investigational formulations (lyophilized versus liquid) and two different PBO formulations (saline versus sorbitol) were employed in the CZP RA program. **Table s6** shows the exposure by investigational formulation and by PBO formulation in the PBO-controlled trials.

Table s6. Exposure by Formulation in PBO-Controlled CZP RA Trials

Extent of Exposure by Formulation Administered - PBO-Controlled Safety Population (Studies 011, 014, 027 and 050)									
	Placebo		CZP 200 mg q2w		CZP 400 mg q2w		CZP 400 mg q4w	All CZP Doses	
	Saline N =324	Sorbital N =228	Lyophilized N =392	Liquid N =249	Lyophilized N =389	Liquid N =246	Lyophilized N =235	Lyophilized N =1016	Liquid N = 494
Mean (SD)	145 (89)	127 (43)	276 (123)	147 (33)	290 (118)	151 (30)	151 (35)	252 (121)	149 (32)
Total Years	128	79	298	100	309	102	97	702	171
# with ≥ 6 months	45 (14%)	5 (2%)	263 (67%)	0	286 (74%)	0	9 (4%)	558 (55%)	202
# with ≥ 12 months	42 (13%)	0	251 (64%)	0	270 (69%)	0	0	521 (51%)	0
# with ≥ 18 months	0	0	0	0	0	0	0	0	0
# with ≥ 24 months	0	0	0	0	0	0	0	0	0
Revised from sponsor Supplement Table 3, pages 9 to 15 of 3877.									

Overall, the demographic and co-morbidities representative of the general RA population were balanced across the treatment groups including the past medical histories and concomitant medications within the studies. In the CZP 400 mg q4w dose regimen studies (with and without concomitant MTX), the patients were generally more ill with more significant past medical history and concomitant medications as compared with q2w + MTX studies.

7.2.2 Explorations for Dose Response

The sponsor conducted Phase 3 trials (011 and 014) which assessed efficacy of the CZP 400 mg q4w. While those trials did show clinical activity, the response rates were lower than those seen with the approved TNF blockers. Subsequently, the sponsor explored the incorporation of a loading dose of 400 mg every 2 weeks x 3 doses followed by 200 mg q2 or 400 mg q2w in the two Phase 3 trials (Study 027 and 050). These data suggest the following: 1) that doses lower than those proposed for approval would likely achieve lower efficacy and 2) that the loading dose of 400 mg q2w for 3 consecutive weeks contributes to efficacy of the proposed maintenance dose regimen.

7.2.3 Special Animal and/or In Vitro Testing

See the Pharmacology Toxicology review by Gary Bond, PhD for this BLA submission. The current labeling reflects the pre-clinical investigations for this study product.

7.2.4 Routine Clinical Testing

The clinical testing across routine hematology and biochemistry tests, and special antibody tests routinely assessed in the management of patients with active RA were employed in these RA trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

The assessment of adequate human pharmacology, bioavailability and bioequivalence parameters were adequate. See the Clinical Pharmacology review by Christoffer Tornoe, PhD and Srikanth Nallani, PhD.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The class of TNF blocking agents treats autoimmune disorders such as RA, ankylosing spondylitis, Crohn's Disease and psoriasis. Treatment with the anti-TNF monoclonal antibody biologics, such as infliximab (Remicade) and adalimumab (Humira) or with the fusion protein etanercept (Enbrel), have a well characterized safety profile. Serious infection, including patients with latent Mycobacterium tuberculosis (TB) infection, possibly developing into active TB, is a risk of TNF inhibitor therapy. The current labeling includes a BOX WARNING: RISK OF SERIOUS INFECTIONS for TB, invasive fungal and other opportunistic infections, some of which have been fatal.

The immune system has a key role in surveillance for malignancy. The role of TNF inhibitors in triggering apoptosis of some tumor cell types has been reported in this class of biologic therapy. Patients with RA, particularly those with highly active RA, are at a higher risk for development of lymphoma. Although there has been no increase in the rate or type of malignancies, there appears to be increased risk for development of lymphoma with TNF inhibitor therapy. Thus, an increased risk of malignancy with chronic long-term TNF inhibition and, specifically, the development of lymphoma is included in the labeling. Injection site reactions represent the most frequent and consistent side effect with TNF administration. These reactions tend to occur early after initiation of treatment and are generally mild and self-limited. TNF inhibitors have also been associated with rare cases of new onset or exacerbation of clinical symptoms of demyelinating disease. In addition, TNF inhibitors have also been reported to result in the formation of auto-antibodies and, rarely, in the development of a lupus-like syndrome.

7.3 Major Safety Results

7.3.1 Deaths

A total of 10 deaths occurred in PBO-controlled studies (9 CZP-treated patients and 1 PBO-treated patient) through the clinical cut-off of January 31, 2007.

In addition, 19 deaths were reported for the OL studies through the safety cut-off of July 15, 2007. This total includes 2 additional deaths in Phase 2 trials (one each in Study 004 and 002). To better understand the cause of death, we examined the narratives for each of the cases. This analysis revealed that many of the deaths judged by the sponsor to be cardiovascular (CVS) actually had an underlying infectious etiology. (See Section 7.7 for 6 additional deaths reported in the 120-Day Safety Update.)

In the PBO-controlled studies, the FDA adjudication for 5 of the 10 deaths differed from the sponsor's final adjudication. As summarized in **Table s7,** infection was the most likely cause of death rather than cardiovascular events in three cases, one with hepatic cirrhosis and cerebrovascular accident as the cause of death in the remaining two cases. Overall, the mortality analysis for the PBO-controlled studies showed 2 cardiovascular deaths, 5 deaths due to infection, one death due to malignancy and one death due to injury in CZP treatment groups. See **Table s8.**

As noted above, there were more deaths in CZP groups than in the PBO group (9 versus 1) in the controlled trials. To understand the risk of death with CZP, we explored exposure-adjusted mortality rates. The total exposure in the All CZP Doses (PBO-controlled) group was 975 pt-yrs. with an incidence of death of 0.94 per 100 pt-yrs. The total exposure in the PBO group was 225 pt-yrs with a death incidence of 0.44 per 100 pt-yrs. The CZP 400 mg q2w + MTX treatment and CZP 200 mg q2w + MTX treatment group showed similar rates.

Looking at this entire safety database (OL as well as controlled studies), the overall mortality rate in All Patients was 0.822 per 100 pt-yrs compared to the mortality rate in the general

population of 0.803 per 100 pt-yrs. The estimated standardized mortality ratio (SMR) for patients receiving CZP as compared to the general population is 1.02 (95% CI 0.67- 1.49) compared to the literature estimates of the SMR in RA patients as 1.27 – 5.56. See **Table s9.**

The time to death from the first dose of study drug ranged from 18 to 980 days. One-third of the patient deaths occurred within 180 days from the first dose.

There were three additional deaths not included in the final adjudication. The first case (Pt. #023/ 23001) was excluded because the death was approximately 5 months post discontinuation of CZP and did not meet the pre-defined inclusion criteria. The second case (Pt. #104/005) was a 65-year old Lithuanian female who died due to disseminated TB. The third case (Pt. #104/ 015) was a 78-year old Lithuanian female who died due to a cardiovascular accident and renal failure. These latter two cases were excluded because of fraud and misconduct at their study site.

Narratives for the 10 deaths (PBO-controlled studies) and the 19 deaths (reported across the OL studies through July 15, 2007) follow after **Table s10** in this review. See Section 7.7 Additional Submissions (120-Day Safety Update) for 6 additional deaths in this submission.

Table s7. Deaths in Placebo-Controlled CZP in RA Studies (Phase 2 and 3)

Adverse Events Leading to Death in PBO-Controlled All CZP RA Studies (Phase 3)				
Patient #, Age/ Sex, Study, Country	CZP Dose/PBO	CZP Exposure to onset of SAE	Cause of Death Per Reviewer	Cause of Death Per CV Safety Committee (b)
088/014 (a) 75/F CZP-027 Latvia	400 mg q2w + MTX Select concomitant: prednisolone, omeprazole	254 days	Infection (Pneumonia with exudative pleuritis, r/o TB)	Possibly cardiovascular origin (b)
114/007 67/M CZP-027 Serbia	200 mg q2w + MTX Select concomitant: meds: prednisolone, diclofenac, amlodipine, ranitidine	125 days	Cardiac arrest	Cardiac arrest (b)
179/001 78/F CZP-027 Belgium	400 mg q2w + MTX Select concomitant meds: aldactazine, IM gold, cimetidine, tramadol, furosemide	15 days 63 dys	Infection (Borreliosis) Cardiac arrest (dilutional hyponatremia, cardiac arrhythmia)	Cardiac arrest (b)
052/002 63/F CZP-027 Croatia	Placebo + MTX Select concomitant meds: prednisolone, ketoprofen, attenolol	104 days	Myocardial infarction	Myocardial infarction (b)
073/003 58/M CZP-027 Hungary	400 mg q2w + MTX Select concomitant meds:prednisolone, leflunomide, indomethacin	112 days	Infection (Empyema: purulent bronchitis, chronic pneumonia)	Myocardial infarction (b)
023/001 (d) 73/F CZP-027 Australia	200 mg q2w + MTX Select concomitant meds: leflunomide, celecoxib, sulfasalz.	129 days	Infection (bacterial peritonitis, ascites)	Hepatic cirrhosis
013/014 (c) 64/F CZP-027 Argentina	400 mg q2w + MTX Select concomitant meds: betamethasone, naproxen.	33 days	Hepatic neoplasm (abnormal abdominal ultrasound)	Hepatitis neoplasm
061/034 83/F CZP-027 Czech Republic	400 mg q2w + MTX Select concomitant meds: ibuprofen	16 days	Infection (acute meningoencephalitis)	Cerebrovascular accident (b)
603/0020 65/F CZP-050 Czech Republic	400 mg q2w + MTX Select concomitant meds TBD	61 days	Injury Femur fracture (complications post-op with shock)	Fracture Shock
133/0018 63/F CZP-050 Serbia	200 mg q2w + MTX Select concomitant meds TBD	146 days	Myocardial infarction Diabetes uncontrolled	Myocardial infarction

a.) Pt.# 088/014 is not reflected in the sponsor's clinical database and does not appear in the sponsor summary tables and figures.
(b.) A total of 7 of 10 deaths were assessed by the CV Safety committee. There were no pre-specified CV endpoints.
(c.) Pt. # 013/004 prematurely withdrew from study-027, prior to receiving the randomized treatment of 400 mg q2w+MTX.
(d.) The death for Pt. #023/001 occurred > 12 wks post the last dose of study medication. The sponsor did not include this patient in the summary tables or Listing 12.1:6 but does include this patient in Listing 12.1:9 and Listing 12.1:10.

Table s8. All Cause Mortality in PBO-Controlled CZP RA Studies

Summary Table - All Cause Mortality CZP Placebo-Controlled RA Clinical Studies Program					
[Studies CZP-002 (iv); CZP-004, -011, -014, -027, -050 (sc); N=1774] **Comparison to Mortality Rates in the Population Exposed to CZP** **1 Death: PBO-Controlled Group ; 9 Deaths: CZP Treatment Groups** Distribution of Cause of Death in Patients Exposed to CZP					
	Number of Observed Cases				
	PBO+ MTX	CZP Doses 200 mg, 400 mg q2w+MTX; 400 mg q4w	Reviewer All CZP Doses	Sponsor All CZP Doses	Expected # of Cases [a]
PBO-Controlled CZP Treatment Group	N=647		N=1774	N=1774	
Cause of Death					
Cardiovascular		2	2	6	10
Infection		5	5	0	1.2
Malignancies		1	1	1	8.4
Injuries (fem frx shock)		1	1	1	2.8
Other non-communicable diseases			0	1	4.6
CZP Treated Patients: TOTAL			9	9	
PBO-Controlled Treatment Group					
Cause of Death					
Cardiovascular	1				
PBO Treated Patients: TOTAL	1				N.A.
OVERALL TOTAL			10	10	
Exposure in Placebo Controlled Studies					
Total Expo. CZP/ PBO-Contr.	957.4 pt-yrs.				
Deaths per 100pt-yrs.	0.94				
Total Expos. PBO-Contr.	224.9 pt.-yrs.				
Deaths per 100pt-yrs.	0.44				
(a.) The number of deaths is compared to the proportion expected in the general population from the World Health Organization (WHO) Burden of Disease database. The crude rates have been adjusted for age. gender, and region from the 2001 data. Table revised from sponsor Table 3:3, page 11 0f 27, Mortality Report.					

Table s9. Incidence of Mortality in RA Patients Exposed to CZP in PBO-Controlled Studies

Incidence of Mortality in RA Patients Exposed to CZP PBO-Controlled Studies						
	PBO-Controlled Studies					All Pts. In CZP RA Studies
	PBO	CZP 200 q2w+MTX	CZP 400 q2w+MTX	CZP 400 q4w	All CZP Doses (PBO-Cont.)	
Total # Patients	**N = 647**	**N = 640**	**N = 635**	**N = 278**	**N = 1774**	**N = 2367**
Total # Deaths (%)	**1 (0.15%)**	**4 (0.6%)**	**5 (0.78%)**	**0**	**9 (0.5%)**	**25 (1.1%)**
Total Exposure, pt.-yrs.	225	396	410	107	957	3284
Deaths per 100 pt.-yrs.	0.44	1	1.2	0	0.94	0.822
Global Mortality Rate in 100 pt-yrs (CZP RA Studies)						0.822
Weighted Mean Mortality Rate in 100 pt-yrs (General Population)						0.803

Note: SMR=Standardized Mortality Ratio; Pop.=Population; pt.-yrs.=patient years; Gen. Pop.= general population; CZP= certoluzimab; MTX=methotrexate; q2w=every 2 weeks; q4w=every 4 weeks. [Note: the far-right column reflects *all* deaths reported in the CZP RA program through 31Nov2007. See Section 7.7 of this review.]

Table s10. Deaths in OL Studies (through 15Jul2007)

Deaths: Open-label Studies through August 31, 2007 (inclusive as known on November 1, 2007)				
CZP Treatment Group Study Site/ Pt.# (Study #) Country	Age/ Sex/R	Event Onset (dys) from 1st Inject.	Prev. Inject.	Cause of Death
PBO/ 20 mg/kg iv (single dose); N=8				
(c.) 004/419 (Study 002) (U.K.	61/F/C	10 days	12 days	RA pericarditis w/effusion (a.)
800 scq4w/ 400 sc q4w; N=39				
(d.) 025/617 (Study 004) U.K.	65/F/C	96	12	Myocardial infarction (a.)
PBO / 400 sc q4w; N=210				
63948/1004 (Study 015) U.S.A.	68M/C	636 days	20 days	Cardiac arrest
63941/1156 (Study 015) U.S.A.	65/M/C	884 days	30 days	Myocardial infarction
56478/1175 (Study 015) Czech Republic	60/F/C	767 days	8 days	Lung cancer w/metastates
PBO+MTX/ 400 sc q4w + MTX; N=210				
78879/1177 (Study 015) Czech Republic	60/M/C	68 days	12 days	Cardiac failure
PBO + MTX / 400 sc q4w; N=210				
79345/1036 (Study 015) Germany	67/F/C	981 days	31 days	Myocardial infarction
PBO+MTX / 400 sc q4w + MTX; N=210				
75225/1138 (Study 015) U.S.A.	65/F/C	659 days	22 days	Injury (car accident,blunt trauma)
400 sc q4w / 400 sc q4w; N=210				
(e.) 53510/1070 (Study 015) U.S.A.	70/F/C	146 days	22 days	Acute myocardial infarction
400 sc q4w+MTX /400 sc q4w+MTX; N=210				
79344/1064 (Study 015) Germany	63/M/C	609 days	23 days	Cardiac failure
69461/1140 (Study 015) U.K.	60/F/C	181 days	22 days	Pneumonia and pneumothorax
69511/1176 (Study 015) Czech Republic	55/F/C	497 days	30 days	Bronchopneumonia
PBO + MTX / 400 sc q2w; N=857				
007/004 (Study 028) Argentina	43/F/H	382 days	4 days	Pulmonary embolism
400 sc q2w + MTX / 400 sc q2w + MTX; N=857				
209/002 (Study 028) Ukraine	64/F/C	252	13 days	Peritoneal infection (a.)
120/029 (Study 051) Poland	34/M/C	282	10 days	Injury, road traffic acident
PBO + MTX / 400 sc q2w + MTX; N=857				
** 101/008 (Study 051) Lithuania	59/M/C	206 days	10 days	Septic shock/Renal failure
200 sc q2w + MTX / 400 sc q2w + MTX; N=582				
133/016 (Study 051) Serbia	68/M/C	291 days	39 days	Cardiopulmonary failure
162/004 (Study 051) Ukraine	54/M/C	171 days	10	Injury, Thermal Burn > 60% BSA

(a.) Fatal events through 31 Dec2006 which were reviewed by the Cardiovascular (CV) Committee.
(b.) Post-clinical cut-off 31Jan2007, 7 additional deaths are reported in Study 028 through the safety cut-off 15Jul2007. The sponsor includes 2 of these 5 deaths in the OL reports (Table 2.7.4:31, page 400 of 973. Hence, 19 deaths (sponsor reports) versus 22 deaths (reviewer reports) in OL studies through 15Jul2007. See Study 028 Report, Section 1.18.2, page 23 of 44 and Safety summary Report, Table 2.7.4:31, page 400 of 973. The sponsor does not include 2 additional deaths in Appendix A, Study 028. See 120-DSU Deaths section of this review.
(c.) Following PBO, Pt. #04/419 (Study 002) received one dose of CZP 20mg/kg i.v.; however, the event which the sponsor reports led to death prior to receipt of CZP treatment.
(d.) Pt. # 25/617 (Study 004) is in the ISS database as having died during the PBO-controlled therapy. The sponsor reports the patient had a chest infection during the PBO control phase.
(e.) Pt. # 53510/1070 is erroneously listed in the ISS database as having died during the PBO-control phase of Study 011. The fatal MI occurred during Study 015.

Narratives - Deaths in PBO-Controlled Studies:

Phase 3 Study 027

Patient # 088/014 (400 mg q2w + MTX group) was a 75-year old Lativan female with a past history of hypertension and osteoporosis. Her Baseline physical examination and chest X-ray were reportedly normal on study entry. She developed serious fatigue after 240 days of CZP exposure at which time her concomitant medications were MTX, prednisolone, omeprazole, perindopril and indapamide. She developed atrial fibrillation with an elevated blood pressure and

was hospitalized with atrial fibrillation with a supraventricular rhythm. An ECG showed ischemia in the latero-apical myocardial wall and repeat ECG showed sinus rhythm with supraventricular and ventricular extra systoles occurring less frequently. She had an ejection fraction of 68% on ECHO and normal CPK-MB values. Based on the above findings, she was diagnosed with chronic heart failure. Fursosemide and spironolactone were added to her medical regimen. CT of her lungs showed pneumonia in the left lower lung with exudative pleuritis. Subsequently, tuberculosis was considered as a possible cause. Though a TB work-up was completed, she was not treated for TB. She was treated with intravenous cefazoline.

Her ECG subsequently worsened with progressive myocardial atrophy compared to her previous ECG with non-specific changes in the myocardial apex. Her ECG worsened with an increased heart rate (120 bpm), ischemia of the myocardial apex, lateral and anterior walls, as well as continued ventricular extra-systoles. Troponin I and T values and CPK-MB were reported normal. She was subsequently discontinued from the study drug. Autoimmune thyroiditis with hypothyroidism was diagnosed as a result of elevated TPO antibodies. No further diagnostic or treatment information was available. She was discharged from the hospital and died a few days later. Causality was possibly related to the serious infection (pneumonia) as the probable cause of death.

Patient #114/007 (200 mg q2w + MTX group) was a 67-year old Serbian male with a past history of arterial hypertension and cardiac risk factors, 55 year history of cigarette smoking and family history of cardiovascular disease. His Baseline vital signs showed mildly elevated BP with an ECG consistent with sinus rhythm, one premature ventricular complex, a flattened T-wave and a negative T-wave in AVL suggestive of asymptomatic myocardial ischemia. After 125 days of the study drug, he died on (b) (6) due to sudden cardiac arrest. No autopsy was performed. Causality was attributed to the patient's underlying cardiovascular condition and pre-existing risk factors.

Patient #179/001 (400 mg q2w + MTX group) was a 78-year old Belgium female with past history of ventricular tachycardia. Her RA deteriorated and the study product was discontinued after two weeks of treatment. She was transferred to the neurology section of a hospital secondary to worsening headache, nausea and vomiting. Serology was positive for *Borrelia*, toxoplasmosis and CMV. Hyonatremia and hypokalemia were reported and a syndrome of inadequate anti-diuretic hormone (SIADH) secretion was suggested for which increasing doses of diuretics were prescribed. Echocardiography reported a sick sinus syndrome of tachy-brady-arrhythmia with intermittent atrial fibrillation, a slight cardiomyopathy and insufficiencies of the aortic, triscupid and mitral valves and aortic valve thickening. The patient died and causality was attributed to the pneumonia.

Patient #052/002 (PBO + MTX group) was a 63-year old Croatian female with a medical history of hypertension. After 104 days in the trial, she experienced severe dyspnea and was reported to die within minutes of this event. No autopsy was performed and the final diagnosis of myocardial infarction was made by the ER staff. Concomitant medications were prednisolone, ketoprofen and attendol. Causality was attributed to the investigational product.

Patient #073/003 (400 mg q2w + MTX group) was a 58-year old Hungarian male with a medical history of hypertension. After receiving 8 injections of study medication, he reported a deterioration in his RA. His gait became unsteady and subsequent X-rays showed a fracture of the left femoral neck. He was discharged from the study after 112 days exposure to CZP. He was hospitalized with a fever and fluid accumulation in the right thoracic cavity due to an empyema. He continued to deteriorate and died approximately one month later. Autopsy revealed recent myocardial necrosis as well as the findings stated above. Causality was attributed to infection (empyema, purulent bronchitis and chronic pneumonia).

Patient #023/001 (200 mg q2w + MTX group) was a 73-year old Australian female who had a pasted history of diabetes mellitus and hypertension. At Baseline, she had elevated ALT (39 IU/ L), AST (57 IU/L) and GGT (77IU/L), as well as an elevated glucose. Her liver function enzymes and blood glucose remain elevated throughout her participation in the study. After 189 days of exposure to the investigational product she was hospitalized due to shortness of breath severe excoriations over her lower abdomen and groin secondary to emphysematous changes, hepatic cirrhosis and ascites. While hospitalized, she experienced a gastrointestinal hemorrhage and received 4 units of red cells as support. She was discharged stable but was readmitted approximately 6 weeks later from a nursing home where she was reportedly found unresponsive to painful stimulation. The cause of death was identified as myocardial infarction. Causality to the investigation product was possible with severe infection (bacterial peritonitis) as the most likely cause of death.

Patient #013/014 (400 mg q2w + MTX group) was a 64-year old Argentinean female with no prior history of neoplasm. Baseline labs showed elevated liver enzymes with an elevated alkaline phosphatase 256 IU/L (normal range 40 - 100 IU/L). Significant hepatomegaly was noted and the patient was discontinued from the investigation product after 2 doses. After 33 days post exposure to CZP, ultrasonography identified a heterogeneous liver with a hypoechogenic node. CT scan confirmed the presence of multiple hepatic tumors with necrosis in the main lesion located in the right side of the liver. The patient died five days after hospitalization. No autopsy was performed. Causality was not attributed to the investigational product. Her death was attributed to the hepatic tumor.

Patient #061/034 (400 mg q2w + MTX group) was a 83-year old Czech female with a past medical history of ischemic heart disease. After 2 CZP injections, she reportedly experienced a cerebral stroke and was hospitalized. She was diagnosed with meningoencephalitis during the hospitalization and died two days post admission. Autopsy reported cerebrovascular accident. An infectious cause of death (meningoencephalitis) as a result of exposure to CZP could not be ruled out as the cause of death.

Phase 3 Study 050

Patient #603/0020 (400 mg q2w + MTX group) was a 65-year old Czech female with a history of osteoarthritis, osteoporosis, chronic ischemic heart disease and hypertension. After she experienced vertigo, she was prescribed pyritinol HCl and naftidrofuryl. The next day, she reportedly suffered a fall and was subsequently hospitalized with a pertrochanteric fracture of the left femur. She underwent surgery for osteosynthesis with repositioning. She died due to

cardiogenic shock and post-operative complications after 71 days exposure to CZP. Causality was not attributed to CZP in view of her traumatic fall and subsequent post-surgical events.

Patient #133/018 (200 mg q2w + MTX) was a 63-year old Serbian female with a history of Type II diabetes mellitus, hypertension and hypercholesterolemia. After 147 days of exposure to CZP, she developed headache, malaise and was hospitalized with worsening hyperglycemia secondary to her diabetes mellitus and was subsequently hospitalized. She improved with insulin and oral hypoglycemic drugs and was reportedly recovered. She also experienced two other non-serious events involving ischemic cardiomyopathy and atrial fibrillation that resulted in her re-hospitalized 39 days later with a severe left-sided pyramidal defect and tachycardia due to atrial fibrillation. After 7 days of hospitalization, she was transferred to a cardiac unit due to an arrhythmia and her condition deteriorated to coma status with and her ECG with an acute anterior wall myocardial infarction. She died 3 days later of acute MI and a cerebrovascular accident. Her death was attributed to CVD in view of her longstanding co-morbid risk factors.

Narratives – Deaths in Phase 2 and OL, Non-PBO-Controlled Studies thru July 15, 2007:
Phase 2 Study 002
Patient #04/419 (20 mg/kg iv, single dose) was a 61-year old British female with a history of severe RA, hypertension and recent chest infection treated with amoxicillin. She developed dyspnea and was hospitalized with pericardial effusion with cardiomegaly. She subsequently had cardiac arrest with extensive cerebral damage and became ventilator dependent. Ventilator support was withdrawn and she died 12 days subsequent to this decision. Causality was attributed to the cardiovascular complications of her severe RA.

Phase 2 Study 004
Patient #025/617 (800 mg q4w/400 mg q4w) was a 65-year old British female with a history of hypertension, hypothyroidism, asthma, gastrointestinal reflux, mitral regurgitation and left ventricular hypertrophy. Concomitant medications were estradiol, norethistrone, levothyrox- ine, rofecoxib, prilosec and ciprofloxacin for a lower respiratory tract infection. After 12 weeks of CZP exposure, she had a fatal MI. Autopsy showed hypertensive myocardiopathy left ventricular hypertrophy, normal pericardium and flecks of atheroma in patent coronary arteries. Pathology showed hypertrophy of the myocardial muscle with focal fibrosis. Causality was attributed to the patient's underlying cardiovascular condition, pre-existing risk factors for CV disease.

OL Study 015
Patient #63948/1004 (PBO/400 mg q4w) was a 68-year old American male with a history of coronary artery disease, MI, chronic obstructive pulmonary disease, atrial pacemaker, hypertension, bullous emphysema, hypercholesterolemia, varicella zoster and tobacco use (2-packs/day). He received PBO in Study 011. Bradycardia and an abnormal ECG without clinical significance were reported 6 months prior to the diagnosis of sinus bradycardia and hypertension (180/90 mmHg). He was hospitalized with chest pain and shortness of breath on exertion and had a positive stress test for reversible ischemia. Cardiac catheterization showed reduced left ventricular function and coronary angiogram showed a normal left main coronary artery, left anterior descending artery with 60% stenosis, left circumflex with 40-50% stenosis and right coronary artery occluded. The ejection fraction was 40% and was managed with antihypertensive

medications. This patient subsequently developed chest pain radiating down his left arm and collapsed. ECG showed ventricular fibrillation and he died despite cardiac resuscitation. Causality was attributed to cardiac arrest as a result of his underlying heart disease and co-morbid risk factors.

Patient #63941/1156 (PBO/400 mg q4w) was a 65-year old American male with a history of coronary artery disease, hypertension and status post esophageal tear repair. He received PBO in Study 011. This patient developed unstable angina after 362 days of exposure to the study product with a positive stress test for inferior lateral ischemia. Cardiac catheterization showed 85% proximal circumflex stenosis and 75% right coronary artery stenosis and an ejection fraction of 60%. A stent was placed and he was discharged from the hospital. While undergoing rehabilitation for knee replacement surgery, he developed a distal esophageal rupture during this hospitalization for the latter and became dizzy, apneic and unresponsive. He died despite resuscitation. No autopsy was performed. Causality was attributed to myocardial infarction in view of his medical history.

Patient #56478/1175 (PBO/400 mg q4w) was a 60-year old Czech female with a history of chronic cigarette smoking. She received PBO in Study 011. After 768 days of exposure to CZP, she developed increases in her LDH, GGT with mild anemia. She was hospitalized and an abdominal ultrasound showed multi-focal hepatopathy; CT scan showed a mediastinal mass with metastatic disease to the liver, lymph nodes and adrenal region. The lymph node biopsy showed necrotizing large cell carcinoma with positive cytokeratin. Cancer markers were reportedly elevated. The patient died secondary to lung cancer. No autopsy was performed. Causality was attributed to the lung cancer with metastases related to her long history of smoking.

Patient #78879/1177 (PBO + MTX/400 mg q4w + MTX) was a 60-year old Czech male with a history of obstructive pulmonary disease, cerebral ischemia, coronary artery disease, hypertension, myocardial infarction, gastric ulcer and psoriasis. Concomitant medications were nitrendipine, oeprazole, rofecoxib, methylprednisolone and MTX. He received PBO in Study 014 and reportedly had an ECG with left ventricular hypertrophy in Study 014. He was reportedly found dead after 68 days of exposure to CZP after enrollment in Study 015. No additional information was reported. Causality was attributed to cardiac failure; however, exposure to CZP could not be excluded as contributing to the cause of death.

Patient #79345/1036 (PBO + MTX/400 mg q4w + MTX) was a 67-year old German female with a history of RA. She had received PBO + MTX in Study 014. The patient experienced phlebitis and thrombosis approximately 4 months after starting exposure to CZP. After 981 days of exposure to CZP she had a fatal myocardial infarction post hospital discharge for a prolapsed vertebral disc. Causality was attributed as myocardial infarction and possibly related to exposure to the investigational product.

Patient #75225/1138 (PBO + MTX/400 mg q4w + MTX) was a 65-year old American female with medical history of hypertension, peripheral neuropathy and lower extremity radiculopathy. Concomitant medications included MTX, naproxen, cyclobenziprine, verapamil, diuretics and axithromycin. The patient was involved in a motor vehicle accident and suffered blunt trauma to

the thorax and head which resulted in death. Causality was attributed to the motor vehicle accident.

Patient #53510/1070 (400 mg q4w/400 mg q4w) was a 70-year old American female with a history of congestive heart failure, pulmonary edema, coronary artery disease, GE reflux, intra-abdominal abscess, pancreatitis, type II diabetes, status post removal of colon polyps, cholecystectomy, Whipple's procedure and right hip replacement. She had received CZP 400 mg q4w in Study 011. Concomitnant medications were celecoxib, acetaminophen/ hydrocodeine, furosemide, ramipril, magnesium and quinine. After 258 days of CZP exposure, the patient suddenly died one morning and was pronounced dead on arrival at the hospital. The cause of death was reported secondary to myocardial infarction attributed to coronary artery disease. Causality was attributed to acute MI that could possibly be related to her exposure to CZP.

Patient #79344/1064 (400 mg q4w + MTX/400 mg q4w + MTX) was a 63-year old German male with medical history of type II diabetes mellitus. Concomitant medications included rofecoxib, prednisolone, MTX and hydromorphine HCl. She received 400 mg q4w + MTX in Study 014. Over the course of Study 014 and Study 015, she complained of mild dizziness and fatigue and was found to have hypertension. After 610 days of CZP exposure, the patient had a cardiac arrest and died. No autopsy was performed. Causality was attributed to cardiac arrest; however, exposure to exposure to CZP could not be ruled out.

Patient #69461/1140 (400 mg q4w + MTX/400 mg q4w + MTX) was a 60-year old British female with a history of chronic obstructive pulmonary disease, recurrent chest infections and hypertension. Concomtantmedications included MTX, fluoxetine, atenolol, ipratropium, bromide, albuterol, celecoxib, nifedipine and paracetamol. The patient was admitted to the hospital intensive care unit with acute symptoms of COPD and was later transferred to another hospital for further care where interstitial pneumonia and fibrosing alveolitis was diagnosed and reportedly considered to be secondary to MTX therapy. Her medical care included ventilation and inotropic support. She subsequently developed a pneumothorax and required was chest drainage. She was diagnosed with end-stage respiratory failure. Inotropic support was withdrawn. She died due to cardiac arrest. Cause of death was determined to be due to be related to infection (pneumonia and the associated pneumothorax) but exposure to CZP could not be excluded as attributing to the infection.

Patient #69511/1176 (400 mg q4w + MTX/400 mg q4w + MTX) was a 55-year old Czech female with a history of cigarette smoking and osteoarthritis. Concomitant medication included MTX, prednisolone, naproxen and famotidine. After 5 months of CZP exposure, she was diagnosed with left side pneumonia which was treated with amoxicillin clavulante. The severe infection required hospitalization due to bilateral pneumonia with dyspnea, basilar crackles, sweating and a productive cough. She was found dead and on autopsy reportedly was found to have catarrhal confluent bronchopneumonia with abscesses. Causality was attributed to broncho-pneumonia but exposure to CZP could not be ruled out as contributing to her cause of death.

OL Study 028

Patient #007/004 (PBO + MTX/ 400 mg q2w) was a 43-year old Argentinean female with a medical history of hypertension, penicillin allergy and gastritis. Concomitant medications included MTX, diclofencac, methylprednisolone and enalapril. She received PBO in Study 027. She was hospitalized and readmitted twice with the diagnosis of herniated lumbar intervertebral disc. She was hospitalized for a third time with tachycardia, tachypnea and abdominal pain and died on the same day of admission. No autopsy was performed. Acute pulmonary embolism was thought to be the cause of death and causality attributed to exposure to CZP could not be ruled out.

Patient #209/002 (400 mg q2w + MTX/400 mg q2w + MTX) was a 64-year old female with a history of ischemic heart disease, extra-systolic arrhythmia, hypertension, varicose veins and thrombophlebitis. Concomitant medication included MTX and methylprednisolone. She was hospitalized with perforated sigmoid colon diverticulum with paracolic abscess and firopurulent peritonitis and underwent resection of the sigmoid colon. During the post-operative period, she developed pneumonia and pulmonary edema as well as cerebral edema and died. No autopsy results were available. Causality was attributed to infection as the cause of death. Exposure to CZP could not be ruled out as associated with this patient's death.

OL Study 051

Patient # 120/029 (400 mg q2w + MTX/400 mg q2w + MTX) was a 34-year old Polish male with a medical history of depression, hypertension and obesity. Concomitant medications at eh time of his demise were MTX, methylprednisolone, diclofencac, Tramadol and omeprazole. After receiving 282 days of CXP exposure, he died in a traffic accident. Cause of death was due to trauma.

Patient #101/0008 (PBO + MTX/400 mg q2w + MTX) was a 59-year old Lithuanian male with a medical history of bronchopneumonia, nephrosclerosis, chronic tubulo-interstitial nephritis, hepatosteatosis, kidney cysts, hepatomegaly and gastric ulcers. He developed high fever and right-sided chest pain and medicated himself with paracetamol. He was hospitalized with anuria, hypertension and in acute distress. He was found to have an elevated creatinine measurement and BUN and chest X-ray was consistent with a non-homogenous infiltration in the right lung. He was diagnosed with severe pneumonia, acute respiratory distress, acute renal insufficiency and septic shock secondary to *Beta-hemolytic Streptococcus,* Group A. He was intubated, remained hemodynamically unstable and died. No autopsy was performed. The cause of death was due to overwhelming infection and causality was attributed to exposure to the investigational study product.

Patient #603/0009 (200 mg q2w + MTX/400 mg q2w + MTX) was a 57-year old Czech female with a history of chronic ischemic heart disease, hypertension, obesity and unspecified gastropathy. Concomitant medications included MTX, methylprednisolone, celecoxib, acetylsalicylic acid, leflunomide, metoprolol and omeprazole. The patient was hospitalized due to decompensation of his left hip with dysplastic deformity, sepsis of this joint and severe RA. He underwent resection of the necrotic left femoral head and the left psoas muscle abscess. Echocardiogram showed a left ventricular fraction of 55% with a pericardial effusion. He

subsequently developed chronic sepsis due to the left hip infection followed by dyspnea and had a cardiac arrest. An autopsy was performed but the results were never made available to the investigator or sponsor.

Patient #133/016 (200 mg q2w + MTX/400 mg q2w + MTX) was a 68-year old Serbian male with a medical history of hematuria, proteinuria, urine calcium oxalate crystals, cardiac arrhythmia, myocardial ischemia and gastritis. Concomitant medications were MTX, flurbipofen, ranitdine, isosorbide amiloride HCl and propaphenone. Hypertension, proteinuria and hematuria were reported after 2 weeks in Study 051. Renal failure and cardiomyopathy were subsequently diagnosed. He went on to develop elevated creatinine, BUN and decreased albumin prior to worsening cardiomyopathy, azotemia and uncontrolled hypertension. Renal ultrasound showed bilateral nephrosclerosis and peritoneal dialysis was initiated. His condition worsened and he developed cardiopulmonary failure which resulted in his death. No autopsy was performed. Cause of death was cardiopulmonary failure secondary to renal failure. Causality was not attributed to the investigational product.

Patient #162/004 (200 mg q2w + MTX/400 mg q2w + MTX) was a 54-year old Ukrainian male with a history only significant for RA. Concomitant medications were MTX and diclofencac. He was involved in an accident which resulted in second and third degree burns and he died despite adequate aggressive medical treatment. The cause of death was complications from severe burns but causality was not attributed to the investigational product.

In summary, although more deaths were observed in CZP groups than in the PBO group (9 versus 1), in the controlled trials, more patients were included in CZP groups and the duration of exposure was longer. When mortality rates were calculated adjusted for exposure the rates were 0.94 per 100 pt-yrs for CZP and 0.44 per 100 pt-yrs for PBO. Mortality rates among CZP-treated patients did not increase with longer duration of exposure. The causes of death were consistent with an increased rate of infection as has been observed in patients exposed to other TNF inhibitors due to suppression of defense mechanisms of the immune system. The incidence of malignancy across these deaths appears consistent with other TNF inhibitors in adults with RA. See Section 7.3.5 Submission Specific Primary Safety Concerns for discussion of malignancy in this review. There were also deaths related to congestive heart failure (CHF) which is prevalent in the RA patient population. The current labeling for CIMZIA® reports that in clinical trials with another TNF inhibitor, cases of new onset and worsening congestive heart failure (CHF) have been observed to be associated with increased mortality due to CHF and that cases of new onset and worsening CHF have also been reported in patients receiving CIMZIA®.

7.3.2 Nonfatal Serious Adverse Events

All safety analyses were performed on the ITT population defined as patients who received at least 1 dose of study medication. All adverse events (AEs) were coded using MedDRA (version 9.0) and were characterized as pre-treatment, post-treatment or treatment-emergent (TEAEs) according to the first intake of the investigational product. Adverse events were reviewed by Primary System Organ Class (SOC) and Preferred Term (PT). Adverse event data for patients who had withdrawn from the ongoing studies as of the safety data cut-off date were included in

the key summaries. For any patient still enrolled in ongoing OL studies at the time of the safety data cut-off, all treatment-emergent adverse event (TEAE) data were reviewed as of the data cut-off. TEAEs were included up to 12 weeks following the last dose of CZP medication. Adverse events starting more than 12 weeks after the last dose of study medication (if reported by the investigator) were not in the pooled data but some have been listed separately

In the PBO-controlled CZP RA trials, there was a higher incidence rate of non-fatal serious adverse events (SAEs) in All CZP treated patients (11%, 20 per 100 pt-yrs) compared with PBO-control patients (7%, 18 per 100 pt-yrs). Overall, the incidence of SAEs in the CZP 200 mg q2w, CZP 400 mg q2w and CZP 400 mg q4w groups were similar, 10%, 11% and 12%, respectively. The more frequent SAEs, in descending order, were Infections and Infestations; Cardiac Disorders; Injury, Poisoning and Procedures; Gastrointestinal Disorders and Neoplasm. All other SOC and PT categories comprise less than 1% of CZP treated patients with the exception of Musculoskeletal and Connective Tissue Disorders which showed between 1.3% and 1.5% incidence of SAEs across each of the CZP treatment groups and the PBO control group.

Infections and infestations showed the highest incidence of SAEs, 4% in All CZP treated patients compared with 0.6% in PBO treated patients. The incidence of SAEs of Infection and Infestations in CZP 200 mg q2w, CZP 400mg q2w and CZP 400mg q4w groups were 4%, 5% and 2%, respectively. Among the PTs, Tuberculosis, lower respiratory tract infections, bacterial infections and upper respiratory tract infections showed 0.5% in the All CZP Doses group compared to 0%, 0.2%, 0%, and 0% in the respective PBO control for each of these PTs. See **Table s11** and Section 7.3.5 Submission Specific Primary Safety Concerns for additional discussion of infections in this submission.

Cardiac Disorders showed the next highest incidence of SAEs with a slightly higher incidence of SAEs in the CZP 400 mg q4w treatment group, 1.1%, compared with 0.8% in both the CZP 200 mg and CZP 400 mg q2w treatment groups. PBO control patients showed 0.5% incidence of cardiac SAEs. There was no cardiac PT which showed a clinically significant number of events in any of the treatment groups. See **Table s11.**

Neoplasm showed an incidence of 0.8% in the All CZP Doses group compared to 0.2%, 1.3%, 0.5% and 0.4% in the PBO control, CZP 200 mg q2w, CZP 400 mg q2w and CZP 400 mg q4w groups. See **Table s11.** Malignancies are considered in more detail below.

A total of 3 CZP treated patients experienced hypersensitivity reactions defined as angioneurotic edema and or urticaria within 14 days of study product administration.

While there was some variation in SAE rates between CZP treatment groups, the incidence of SAEs increased with higher doses of CZP was not meaningful. In general, the SOCs and the incidences in which the SAEs were observed most commonly were consistent with safety outcomes reported with other TNF inhibitors.

Table s11. Serious Adverse Events in PBO-Controlled Studies in CZP RA Program

Serious Adverse Events (SAEs) ≥ 0.3 % - All CZP PBO-Controlled Studies in RA					
System Organ Class (SOC) Preferred Term (PT)	PBO N = 647	CZP 200 mg q2w N = 640	CZP 400 mg q2w N = 635	CZP 400 mg q4w N =278	All CZP Doses N = 1774
Total Exposure, Patient Yrs.	225	396	410	107	957
# Pts with SAE., pt. %)	42 (7%)	65 (10.2%)	67 (11%)	32 (11.5%)	189 (10.7%)
Total SAEs	57	90	103	49	284
Blood and Lymphatic System	0	4 (0.6%)	2 (0.3%)	1 (0.4%)	8 (0.5%)
Anemia	0	2 (0.3%)	0	0	2 (0.1%)
Lymphadenopathy mediastinal	0	1 (0.2%)	0	0	1 (0.1%)
Pancytopenia	0	0	1 (0.2%)	1 (0.4%)	2 (0.1%)
Cardiac Disorders	3 (0.5%)	5 (0.8%)	5 (0.8%)	3 (1.1%)	16 (0.9%)
Acute myocardial infarction	1 (0.2%)	2 (0.3%)	1 (0.2%)	0	3 (0.2%)
Angina pectoris	0	1 (0.2%)	0	1 (0.4%)	2 (0.1%)
Cardiac arrest	0	1 (0.2%)	1 (0.2%)	0	2 (0.1%)
Gastrointestinal disorders	4 (0.6%)	3 (0.5%)	5 (0.8%)	4 (1.4%)	13 (0.7%)
Abdominal pain	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.4%)	3 (0.2%)
Nausea	2 (0.3%)	0	1 (0.2%)	0	1 (0.1%)
Vomiting	2 (0.3%)	0	1 (0.2%)	0	2 (0.1%)
General Disorders, Admin. Site	5 (0.8%)	2 (0.3%)	2 (0.3%)	3 (1.1%)	10 (0.6%)
Pyrexia	1 (0.2%)	2 (0.3%)	1 (0.2%)	1 (0.4%)	5 (0.3%)
Injection site pain	1 (0.2%)	0	0	1 (0.4%)	2 (0.1%)
Hepatobiliary Disorders	0	4 (0.6%)	3 (0.5%)	0	7 (0.4%)
Cholelithiasis	0	2 (0.3%)	2 (0.3%)	0	4 (0.2%)
Infections and Infestations	4 (0.6%)	24 (3.8%)	29 (4.6%)	5 (1.8%)	62 (3.5%)
Tuberculosis infections	0	5 (0.8%)	4 (0.6%)	0	9 (0.5%)
Disseminated TB	0	3 (0.5%)	1 (0.2%)	0	4 (0.2%)
Tuberculosis	0	0	2 (0.3%)	0	2 (0.1%)
Lower respir. tr., lung infects	1 (0.2%)	3 (0.5%)	5 (0.8%)	0	9 (0.5%)
Pneumonia	0	3 (0.5%)	4 (0.6%)	0	8 (0.5%)
Abdominal, GI infections	1 (0.2%)	2 (0.3%)	1 (0.2%)	0	3 (0.2%)
Appendicitis	0	1 (0.2%)	1 (0.2%)	0	2 (0.1%)
Bacterial infections NEC	0	2 (0%)	4 (0.6%)	1 (0.4%)	8 (0.5%)
Cellulitis	0	1 (0.2%)	2 (0.3%)	1 (0.4%)	5 (0.3%)
Arthritis bacterial	0	0	3 (0.2%)	0	3 (0.2%)
Skin, soft tissue infections	0	2 (0.3%)	0	0	2 (0.1%)
Subcutaneous abscess	0	2 (0.3%)	0	0	2 (0.1%)
Upper respir. tract infections	0	2 (0.3%)	5 (0.6%)	1 (0.4%)	9 (0.5%)
Sinusitis	0	1 (0.2%)	3 (0.5%)	0	4 (0.3%)
Urinary tract infections	0	2 (0.3%)	3 (0.5%)	0	6 (0.3%)
Pyelonephritis	0	1 (0.2%)	0	0	2 (0.1%)
Pyelonephritis, acute	0	1 (0.2%)	2 (0.3%)	0	3 (0.2%)
Herpes viral infection	0	1 (0.2%)	1 (0.2%)	0	2 (0.1%)
Herpes zoster	0	1 (0.2%)	1 (0.2%)	0	2 (0.1%)
Infections NEC	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (0.4%)	4 (0.2%)
Sepsis, bacteriemia, viremia	0	1 (0.2%)	1 (0.2%)	0	3 (0.2%)
Streptococcal infections	1 (0.2%)	1 (0.2%)	5 (0.8%)	0	6 (0.3%)
Erysipleas	1 (0.2%)	1 (0.2%)	5 (0.8%)	0	6 (0.3%)
Injury, poisoning, procedures	4 (0.6%)	5 (0.8%)	8 (1.3%)	2 (0.7%)	16 (0.9%)
Fractures and dislocations NEC	1 (0.2%)	1 (0.2%)	0	1 (0.4%)	2 (0.1%)
Lower limb frx, dislocations	1 (0.2%)	1 (0.2%)	4 (0.6%)	0	5 (0.3%)
Femur frx	0	0	2 (0.3%)	0	2 (0.1%)
Limb injuries (menis, synov. rup.)	0	0	1 (0.2%)	0	2 (0.1%)

Revised from sponsor Table 30, pages 2927 to 3099 of 3877.

Table s11. (Continued) Serious Adverse Events in PBO-Controlled Studies in CZP RA Program

Serious Adverse Events (SAEs) ≥ 0.3 % - All CZP PBO-Controlled Studies in RA					
System Organ Class (SOC) Preferred Term (PT)	PBO N = 647	CZP 200 mg q2w N = 640	CZP 400 mg q2w N = 635	CZP 400 mg q4w N =278	All CZP Doses N = 1774
Investigations	3 (0.5%)	1 (0.2%)	1 (0.2%)	0	5 (0.3%)
Respir. tr. thorac. imag. proce.	0	1 (0.2%)	0	0	2 (0.1%)
Chest X-ray abnormal	0	1 (0.1%)	0	0	2 (0.1%)
Liver function analyses	1 (0.2%)	0	1 (0.2%)	0	2 (0.1%)
Musculoskeletal, CTD disorders	10 (1.5%)	10 (1.6%)	8 (1.3%)	5 (1.8%)	31 (1.7%)
Rheumatoid arthropathies	5 (0.8%)	4 (0.6%)	2 (0.3%)	5 (1.8%)	14 (0.8%)
Rheumatoid arthritis	5 (0.8%)	4 (0.6%)	2 (0.3%)	5 (1.8%)	14 (0.8%)
Bone disorders NEC	0	2 (0.3%)	1 (0.2%)	0	3 (0.2%)
Osteonecrosis	0	2 (0.3%)	1 (0.2%)	0	3 (0.2%)
Musculoskeletal , CT sx, sy NEC	2 (0.3%)	0	2 (0.3%)	0	2 (0.1%)
Synovial disorders NEC	2 (0.3%)	0	1 (0.2%)	0	4 (0.2%)
Neoplasms	1 (0.2%)	8 (1.3%)	3 (0.5%)	1 (0.4%)	14 (0.8%)
Basal cell carcinoma	0	2 (0.3%)	0	0	2 (0.1%)
Colon cancer	0	0	2 (0.2%)	0	2 (0.1%)
Nervous System Disorders	5 (0.8%)	3 (0.5%)	3 (0.5%)	4 (1.4%)	11 (0.6%)
CNS hemorrhages, CVAs	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (0.4%)	4 (0.2%)
Cerebrovascular accident	1 (0.2%)	1 (0.2%)	2 (0.3%)	0	3 (0.2%)
Transient ischemic attack	0	1 (0.2%)	1 (0.2%)	0	2 (0.1%)
Renal and urinary disorders	2 (0.3%)	3 (0.5%)	1 (0.2%)	2 (0.7%)	7 (0.4%)
Reproduct. system, breast dis.	0	4 (0.6%)	2 (0.3%)	2 (0.7%)	8 (0.5%)
Menorrhagia	0	1 (0.2%)	0	1 (0.4%)	2 (0.1%)
Respiratory, thoracic, medias.	4 (0.6%)	1 (0.2%)	6 (0.9%)	0	7 (0.4%)
Lung infiltration	0	1 (0.2%)	2 (0.3%)	0	3 (0.2%)
Pleurisy	0	0	2 (0.3%)	0	2 (0.1%)
Skin, subcutaneous tiss. Dis.	0	0	1 (0.2%)	3 (1.1%)	6 (0.3%)
Angioneurotic edema	0	0	0	1 (0.4%)	1 (0.1%)
Rash	0	0	0	2 (0.7%)	2 (0.1%)
Urticaria	0	0	0	2 (0.4%)	1 (0.1%)
Surgical, medical procedures	2 (0.3%)	1 (0.2%)	0	3 (1.1%)	7 (0.4%)
Synovectomy	0	0	0	1 (0.4%)	2 (0.1%)
Vascular Disorders	0	2 (0.3%)	4 (0.6%)	2 (0.7%)	9 (0.5%)
Hypertension	0	1 (0.2%)	0	1 (0.4%)	2 (0.1%)
Hypertensive crisis	0	0	0	1 (0.4%)	1 (0.1%)
Deep vein thrombosis	0	0	1 (0.2%)	0	2 (0.1%)

Revised from sponsor Table 30, pages 2927 to 3099 of 3877.

7.3.3 Dropouts and/or Discontinuations

Overall, in the PBO-controlled studies, patients withdrew due to the development of an AE more frequently in the CZP treatment groups than in the PBO group. Approximately 5% of patients in each of the CZP groups withdrew due to an AE compared to 2.5% with PBO. See **Table s12.**

Infections and Infestations was the most frequent category of TEAEs leading to withdrawal (2% in the All CZP Doses group compared 0.2% with PBO control). Disseminated tuberculosis and tuberculosis were the most common infections causing withdrawal in CZP treated patients. Pneumonia was another infection leading to withdrawal in CZP treated patients. See **Table s12.**

Skin and Subcutaneous Tissue Disorders showed the most frequent category of TEAEs leading to patient withdrawal in the PBO controlled studies among the CZP treated patients, (0.7%) versus 0% with PBO. The majority of PT AEs in this SOC were reported as rash. See **Table s12.**

Table s12. Summary of AEs Leading to Withdrawals in PBO-Controlled Studies

Summary of Overall All Adverse Events in PBO-Controlled CIMZIA in RA Studies					
	PBO	CZP 200 mg q2w+MTX	CZP 400 mg q2w+MTX	CZP 400 mg q4w	All CZP Doses
Enrolled	N=647 n (%)	N=640 n (%)	N=635 n (%)	N=278 n (%)	N=1774 n (%)
Total Exposure in Patient-Years	225	398	410	107	957
# Pts with any AE	404 (62%)	433 (68%)	425 (67%)	216 (78%)	1258 (71%)
Total # AEs	1372	1852	1859	812	5331
Serious AEs	42 (7%)	65 (10%)	67 (11%)	32 (12%)	189 (11%)
AEs leading to Death	1 (0.2%)	4 (0.6%)	5 (0.8%)	0	9 (0.5%)
AEs leading to Withdrawal	N=552 14 (2.5%)	N=640 31 (4.8%)	N=635 31 (4.9%)	N=235 13 (5.5%)	N=1510 75 (5%)
Note: CZP=certolizumab pegol; q2w=every 2 weeks; q4w = every 4 weeks; MTX=methotrexate; mg=milligrams. Revised from sponsor table 2.5:8, page 33 of 52 and Table 8.1:10 pages 89 to 297 of 13991.					

Table s12. *Continued* Summary of AE ≥ 0.5 % leading to Withdrawal in PBO-Controlled Studies

Summary of Adverse Events > 0.3 % Leading to Withdrawal in PBO-Controlled Studies (Safety Population)					
Primary SOC, PT	PBO + MTX N = 552	CZP 200 mg q2w +MTX N = 640	CZP 400 mg q2w + MTX N = 635	CZP 400 mg q4w N = 235	All CZP Doses N = 1510
# Adverse Events (# pts., %)	14 (2.5%)	31 (4.8%)	31 (4.9%)	13 (5.5%)	75 (5%)
Total AEs	18	43	36	23	102
Blood and lymphatics	0	3 (0.5%)	1 (0.2%)	0	4 (0.3%)
Cardiac disorders	1 (0.2%)	4 (0.6%)	2 (0.3%)	0	6 (0.4%)
Acute myocardial infarction	1 (0.2%)	1 (0.2%)	1 (0.2%)	0	2 (0.1%)
Gastrointestinal disorders	2 (0.4%)	1 (0.2%)	3 (0.5%)	0	4 (0.3%)
Gen. disorders and administr. site conditions	0	5 (0.8%)	2 (0.3%)	1 (0.4%)	8 (0.5%)
Pyrexia	0	4 (0.6%)	0	1 (0.4%)	5 (0.3%)
Infections and infestations	1 (0.2%)	12 (1.9%)	10 (1.6%)	5 (2.1%)	27 (1.8%)
Disseminated TB	0	3 (0.5%)	1 (0.2%)	0	4 (0.3%)
Tuberculosis	0	0	2 (0.3%)	0	2 (0.1%)
Pneumonia	0	1 (0.2%)	3 (0.5%)	0	4 (0.3%)
Investigations	2 (0.4%)	0	0	2, 0.9%)	2 (0.1%)
ALT increased	0	0	0	1 (0.4%)	1 (0.1%)
AST increased	0	0	0	1 (0.4%)	1 (0.1%)
Renal function test abnormal	0	0	0	1 (0.4%)	1 (0.1%)
Neoplasms	2 (0.4%)	5 (0.8%)	2 (0.3%)	0	7 (0.5%)
Nervous system disorders	0	1 (0.2%)	1 (0.2%)	2 (0.9%)	4 (0.3%)
Headache	0	0	0	2 (0.4%)	2 (0.1%)
Respiratory, thoracic and mediastinal disorders	3 (0.5%)	0	2 (0.3%)	0	2 (0.1%)
Pleurisy	0	0	2 (0.3%)	0	2 (0.1%)
Skin and subcutaneous tiss.	0	2 (0.3%)	5 (0.8%)	4 (1.7%)	11 (0.7%)
Rash	0	1 (0.2%)	0	3 (1.3%)	4 (0.3%)
Rash vesicular	0	0	1 (0.2%)	0	1 (0.1%)
Urticaria	0	1 (0.2%)	2 (0.3%)	1 (0.4%)	4 (0.3%)
Angioneurotic edema	0	0	0	1 (0.4%)	1 (0.1%)
Dermatitis allergic	0	0	3 (0.5%)	0	3 (0.2%)

Revised from Source Table 8.1:32, pages 4,555 to 4,586 of 13,991

Methotrexate and Patient Withdrawals

Methotrexate therapy is a known risk factor for infection. Therefore we explored whether concomitant use of MTX with CZP increased the risk of infection. **Table s13** examines significant infections, defined as those classified as severe or serious or those leading to withdrawal. As expected, the rate of significant infection was higher, overall, with CZP (38%) than with PBO (23%). Infections were not more frequent in the studies with concomitant MTX than with CZP monotherapy.

Table s13. Overview: Infections Leading to Withdrawal in the PBO-Controlled CZP RA Studies

Severe Infections, Serious Infections and Infections Leading to Withdrawal - PBO-Controlled Studies					
All Studies	PBO N =647	CZP 200 mg [(a.)] q2w N =640	CZP 400 mg q2w N =635	CZP 400 mg q4w N =278	All CZP Doses N = 1774
Exposure in pt.-yrs.	225	396	410	107	957
Any Infection	232 (148,23%)	443 (239, 37.3%)	437 (239, 37.6%)	141 (103, 37.1%)	1146 (667, 37.6%)
Any WD due to Infection	1 (1, 0.2%)	14 (12, 1.9%)	10 (10, 1.6%)	8 (5, 1.8%)	39 (27, 1.8%)
MTX Studies	N = 443	N =640	N =635	N =124	N = 1399
Any Infection	175 (105, 23.7%)	443 (239, 37.3%)	437 (239, 37.6%)	71 (50, 40.3%)	951 (528, 37.7%)
Any WD due to Infection	1 (1, 0.2%)	14 (12, 1.9%)	10 (10, 1.6%)	6 (3, 2.4%)	30 (25, 1.8%)
Non-MTX Studies	N = 204			N = 154	N =375
Any infection	57 (43, 21.1%)			70 (53, 34.4%)	195 (139, 37.1%)
Any WD due to infection	0			2 (2, 1.8%)	2 (2, 1.8%)

(a.) Following 3 loading doses of CZP 400 mg each. Revised from sponsor Table 2.7.4:35, page 441 of 973

Concomitant Corticosteroids with CZP

Concomitant corticosteroid use is also a known risk factor for infection. In the PBO controlled studies in the All Doses CZP group, there was a higher incidence of infectious SAEs (40%) in corticosteroid CZP treated patients compared with non-corticosteroid treated patients (35%). These data suggest that corticosteroid use may increase the rate of serious infection in CZP-treated patients; however, the difference in rates is too small to make a firm conclusion.

Investigational Formulations and Patient Withdrawals

The sponsor conducted three Phase 3 trials (027, 011 and 014) using a lyophilized formulation, which is the approved, marketed product for the Crohn's disease indication. Subsequently, they conducted one Phase 3 trial (050) in RA with a liquid formulation. Since the sponsor proposes to market the liquid formulation, it is important to determine whether there is any evidence of increased toxicity with the liquid formulation.

A higher percentage of lyophilized CZP 200 mg q2w treated patients experienced TEAEs (75%) than did patients treated with the liquid formulation CZP 200 mg q2w (56%). Patients treated with CZP 400 mg q2w lyophilized formulation had a 77% incidence of AEs compared with 51% with the CZP 400 mg q2w liquid formulation. See **Table s14.**

More frequent SAEs were observed with the lyophilized versus the liquid formulation administered as CZP 200 mg q2w, 12% versus 8% incidence of SAEs, respectively. Similarly, the lyophilized CZP 400 mg q2w group had a higher incidence of TEAEs (13%) compared with the liquid CZP 400 mg q2w treatment group (7%).

Overall, the AEs which led to withdrawal were similar between CZP 200 mg q2w lyophilized versus liquid formulation groups (5%, respectively. In CZP 400 mg q2w group, the lyophilized group experienced a higher incidence of AEs (6%) compared to the liquid formulation (3%). In CZP 400 mg q4w group, the lyophilized formulation showed a higher incidence of AEs leading to withdrawal (6%) that was similar to the trend seen with CZP 200 mg q2w dose regimen. In

summary, the proposed liquid formulation appeared to show fewer overall AEs and AEs leading to withdrawal compared with the lyophilized formulation.

There were a higher percentage of patients with AEs leading to withdrawal in the sorbitol PBO group (4%) compared with the saline PBO group (2%) which was accounted for by injection site reactions due to sorbitol. A similar trend with increased SAEs with sorbitol PBO (8%) compared with (5%) saline PBO was also shown in **Table s14.** The duration of exposure for the saline PBO was higher by approximately 1.6 times than with the sorbitol PBO although there were more AEs shown with the sorbitol formulation. This outcome may be attributed to the viscosity of the sorbitol formulation.

Table s14. Adverse by Formulation (lyophilized versus liquid) in CZP RA Studies

Summary of AEs by Formulation - Study 011, -014, -027 and -050 - PBO-Controlled Data in RA									
	Placebo		CZP 200 mg [a] q2w		CZP 400 mg q2w		CZP 400 mg q4w	All CZP Doses	
	Saline N = 324	Sorbital N =228	Lyophil. N =392	Liquid N = 248	Lyophil. N = 389	Liquid N =246	Lyophil. N = 235	Lyophil. N = 1016	Liquid N = 494
Any AE	181 (56%)	146 (64%)	294 (75%)	139 (56%)	299 (77%)	126 (51%)	182 (77%)	775 (76%)	265 (54%)
Serious AE	16 (5%)	18 (8%)	45 (12%)	20 (8%)	49 (13%)	18 (7%)	24 (10%)	118 (12%)	38 (8%)
Events Leading to Withdrawal	9 2%)	8 (4%)	18 (5%)	13 (5%)	23 (6%)	8 (3%)	13 (6%)	54 (5%)	21 (4%)

(a.) Following 3 loading doses of 400 mg each. CZP=certoluzimab pegol; q2w=every 2 weeks; q4w=every 4 weeks; lyophil = lyophilized. Data reported as number of patients. Revised from sponsor Table 2.7.4:28, page 393 of 973

7.3.4 Significant Adverse Events

See Section 7.3.5 Specific Primary Safety Concerns below for review of the significant adverse events in this submission.

7.3.5 Submission Specific Primary Safety Concerns

All Infections, Non-Serious and Serious

There was a higher incidence of infection in the ALL CZP Doses group (38%) compared to the PBO control (23%). The same spectrum of infections were most often reported by both the ALL CZP Doses group of patients and PBO patients as follows: upper respiratory tract infections (18% in the All CZP Doses group versus 10% in PBO-control); nasopharyngitis (6% in the All CZP Doses group versus 3% in PBO control); urinary tract infections (6% incidence in the All CZP Doses group versus 5% in PBO control); lower respiratory tract infections and lung infections, 6% in the All CZP Doses group versus 3% in PBO control. See **Table s15.**

The CZP treatment was associated with a higher incidence of upper respiratory tract infections, nasopharyngitis and the category recorded as bacterial infections. There was no evidence of a dose response with the CZP doses tested.

Table s15. All Infections and Infestations AEs in PBO-Controlled RA Safety Population

Infections Occurring in ≥ 2% of Patients - PBO-Controlled Studies					
High Level Term *Preferred Term*	PBO N = 647	CZP 200 mg [a.] q2w N = 640	CZP 400 mg q2w N = 635	CZP 400 mg q4w N = 278	All CZP Doses N = 1774
Exposure in pt.-yrs.	225	396	410	107	957
Any Event in SOC Infections and Infestations	148 (23%)	239 (37.3%)	239 (37.6%)	103 (37.1%)	667 (37.6%)
Upper respir. tr. Infections	61 (9%)	107 (17%)	101 (16%)	55 (20%)	313 (18%)
Upper respirat. tr. Infection	18 (3%)	35 (6%)	25 (4%)	17 (6%)	89 (5%)
Nasopharyngitis	22 (3%)	29 (5%)	34 (5%)	23 (8%)	108 (6%)
Pharyngitis	5 (0.8%)	20 (3%)	16 (2.5%)	2 (0.7%)	43 (2.4%)
Sinusitis	9 (1.4%)	14 (2.2%)	10 (1.6%)	10 (3.6%)	37 (2.1%)
Rhinitis	4 (0.6%)	13 (2%)	11 (1.7%)	3 (1.1%)	38 (2.1%)
Urinary tract infections	29 (4.5%)	33 (5.2%)	38 (6%)	4 (1.4%)	84 (4.7%)
Urinary tract infection	26 (4%)	37 (5.8%)	37 (5.8%)	14 (5%)	100 (5.6%)
Lower respir. tr., lung infect.	22 (3.4%)	37 (5.8%)	37 (5.8%)	14 (5%)	100 (5.6%)
Bronchitis acute	4 (0.6%)	19 (3%)	22 (3.5%)	1 (0.4%)	44 (2.5%)
Bronchitis	11 (1.7%)	9 (1.4%)	7 (1.1%)	9 (3.2%)	28 (1.6%)
Bacterial infections NEC	11 (1.7%)	26 (4.1%)	29 (4.6%)	1 (0.4%)	59 (3.3%)
Bactiuria	7 (1.1%)	14 (2.2%)	16 (2.5%)	0	31 (1.7%)
Viral infections NEC	8 (1.2%)	25 (3.9%)	19 (3%)	2 (0.7%)	47 (2.6%)
Herpes viral infections	8 (1.2%)	20 (3.1%)	26 (4.1%)	10 (3.6%)	63 (3.6%)
Herpes simplex	5 (0.8%)	16 (2.5%)	18 (2.8%)	9 (3.2%)	50 (2.8%)
Infections NEC	6 (0.9%)	19 (3%)	13 (2%)	3 (1.1%)	38 (2.1%)
Respiratory tr. Infections	1 (0.2%)	15 (2.3%)	7 (1.1%)	1 (0.4%)	24 (1.4%)
Influenza viral infections	9 (1.4%)	18 (2.8%)	6 (0.9%)	6 (2.2%)	32 (1.8%)
Influenza viral infections	9 (1.4%)	18 (2.8%)	6 (0.9%)	6 (2.2%)	32 (1.8%)

(a.) Following 3 loading doses of CZP 400 mg each. CZP=certoluzimab pegol; NEC= not elsewhere classified; tr.=tract; infect.=infections; respir.=respiratory. Data are presented as number of patients (percent of patients).
Revised from sponsor Table 2.7.4:37, page 442 of 973

Cardiovascular

No evidence of a cardiac signal with CZP treatment was observed. Cardiac TEAEs leading to withdrawal were similar in the All CZP Doses versus PBO-control group (0.4% versus 0.2%). There was no evidence of a dose-related effect on the cardiac TEAEs with CZP.

In the All CZP Doses group, the most common cardiovascular event compared to PBO-control was Vascular Hypertensive Disorders NEC (5% versus 1.2%), Rate and Rhythm Disorders (1% versus 0.2%), Ischemic Coronary Artery Disorders (0.7% versus 0.3%), Peripheral Embolism and Thrombosis (0.6% versus 0%) and Supraventricular Arrhythmias (0.6% versus 0.5%). Although these data indicate a higher rate of hypertensive TEAEs with CZP compared to PBO controls, no increase in the mean blood pressure over time was observed in CZP-treated patients. Furthermore, there was no pattern of hypertensive SAEs or cardiovascular SAEs observed in CZP treated patients.

A small number of Heart Failure TEAEs were observed in CZP treated patients in the PBO-controlled studies and extension studies. In the PBO-controlled studies and the OL studies, the Heart Failure SAEs incidence rate was 0.18 per 100 pt-yrs. In the PBO-control studies, one patient had a Cardiac Failure SAEs (0.10 per 100 pt-yrs). Overall, the risk of serious heart failure did not appear to increase with long-term CZP exposure.

In summary, there was no cardiovascular signal in this safety database for CZP in RA. These findings are consistent with what has been observed with other TNF inhibitors.

Serious Infections

The pre-specified definition of an SAE for infection included but was not limited to any infection requiring parenteral antibiotics. The All CZP Doses group showed a higher incidence of SAEs due to infections (4%, 6.69 per 100 pt-yrs) compared with PBO control (0.6%, 1.65 per 100 pt-yrs). Tuberculosis (0.5%), bacterial infections NEC (0.5%), upper respiratory tract infections (0.5%) and lower respiratory tract and lung infections (0.5%) were the four most frequently reported infectious SAEs (≥ 0.5%) in the All CZP Doses groups as shown in **Table s16.** There was no single infectious SAE observed by more than one patient in the PBO control group.

Table s16. SAEs: Infections and Infestations in PBO-Controlled CZP RA Trials

Infections - All Serious AEs - PBO-Controlled Studies RA Safety Population					
	PBO N =647	CZP 200 mg q2w N = 640	CZP 400 mg q2w N =635	CZP 400 mg q4w N = 278	All CZP Doses N = 1774
Infections and Infestations	4 (4, 0.6%)	25 (24, 3.8%)	35 (29. 4.6%)	7 (5, 1.8%)	73 (62, 3.5%)
Tuberculosis infects.	0	5 (5, 0.8%)	4 (4, 0.6%)	0	9 (9, 0.5%)
Disseminated TB	0	3	1	0	4
Peritoneal TB	0	1	0	0	1
Pulmonary TB	0	1	0	0	1
Lymph Node TB	0	0	1	0	1
Tuberculosis infects.	0	0	2	0	2
Lower respir. tr. and lung infects.	1 (1, 0.2%)	3 (3, 0.5%)	5 (5, 0.3%)	0	9 (9, 0.5%)
Pneumonia	0	3	4	0	8 (8, 0.5%)
Lower respir. tr. Infect	1	0	0	0	1 (1, 0.1%)
Obstructive chronic bronchit. with acute exacerbation	0	0	1		
Abdominal , GI infects.	1 (1, 0.1%)	2 (2, 0.3%)	1 (1, 0.2%)	0	3 (3, 0.2%)
Bacterial infects.	0	2 (2, 0.3%)	6 (4, 0.6%)	3 (1, 0.4%)	12 (8, 0.5%)
Skin, soft tissue infects.	0	3 (2, 0.3%)	0	0	3 (2, 0.1%)
Upper respir. Tr infects.	0	2 (2, 0.3%)	5 (4, 0.6%)	1 (1, 0.4%)	9 (8, 0.5%)
Urinary tr. Infects.	0	2 (2, 0.3%)	3 (3, 0.5%)	0	6 (6, 0.3%)
Dental, oral soft tiss. Infects.	0	1	0	0	1 (1, 0.1%)
Hepatitis viral infects.	0	1	0	0	1 (1, 0.1%)
Herpes viral infects.	0	1	1	0	2 (2, 0.1%)
Infections NEC	1	1	2	1	4 (4, 0.2%)
Sepsis, bacteremia, viremia	0	1	1	0	3 (3, 0.2%)
Streptococcal infects.	1	1	5 (5, 0.8%)	0	6 (6, 0.3%)
Breast infects.	0	0	0	1	1 (1, 0.1%)
CNS, spinal infects.	0	0	0	1	1
Ear infects.	0	0	1 (1, 0.2%)	0	1 (1, 0.1%)
Legionella infects.	0	0	0	0	1 (1, 0.1%)
Papilloma viral infects.	0	0	1 (1, 0.2%)	0	1 (1, 0.1%)

Revised from sponsor Table 8.1:22, page 3,660 to 3,722 of 13,991

Overall Long-Term Infection

In the All Studies RA Population, the rate of infections did not increase with increased exposure to CZP. With long-term therapy, the incidence of infection SAEs per 100 pt.-yrs in All CZP Doses group decreased (6.69, PBO control versus 5.39, across All Studies).

Tuberculosis

There was no systematic screening for *M. tuberculosis* in the early development of CZP in RA. The healthy volunteer Studies (001, 003, PHA-024 and 038) did not require a chest X-ray or PPD testing to be done as part of the screening procedures. In Studies 002, 004 and PHA-001 only chest X-rays performed for study entry. Subsequently, PPD testing and chest X-rays were added to the Phase 3 studies but the administration and interpretation of the PPD test was based on local standards of care. In BCG-vaccinated areas (e.g. France and Eastern Europe) patients with PPD induration ≥ 5mm needed higher thresholds, e.g. ≥ 5 to 10 mm to participate in CZP trials without TB prophylaxis based on the assumption that these results were due to previous vaccination with BCG.

In the CZP RA trials the diagnosis of tuberculosis (TB) was based on the presence of classical symptoms (e.g, asthenia, cough and fever), new abnormalities in a chest X-ray, and sputum microscopy or culture. A total of 23 patients in the CZP RA studies developed TB through the cut-off of 31Jan07: 11 patients with pulmonary TB; 9 patients with disseminated TB; 2 patients with lymph node TB and 1 patient with pleural TB.

All but one of the CZP treated patients who developed TB over the course of the studies was receiving concomitant MTX. In addition, 14 of these 23 patients were receiving concomitant corticosteroids. The onset of TB was observed after 12 weeks of CZP treatment in 18 of 23 patients out of which 2 cases reported recent close contacts with TB.

Across all CZP clinical development programs, a total of 5,118 patients were exposed to the study product representing 6,405 pt-yrs out of which 35 cases of TB (14 confirmed) were reported. This is approximately 6,405 pt.-yrs and approximately 5.46 cases per 100 pt-yrs [95% CI: 381-760]. Of these 35 cases, a total of 26* cases were observed in the CZP RA studies in which 2,367 patients were exposed. For the proposed RA indication safety database, the TB incidence rate was approximately 1.1% in patients treated with CZP. See **Table s17.** * A total of 30 patients with TB were observed in the CZP RA studies including the 120DSU safety data through safety cut-off of 01Nov2007.

Three additional cases were reported as of 04Oct2007 and were included in the All CZP studies safety database. Two fatal cases were observed involving one patient (# 212/008) from the site in Lithuania where fraud and misconduct was reported, and one additional Patient # 2371. Three cases, Patient # 865 (CIOMS # 8018046); Patient # 248 (CIOMS # 8020376); and Patient # 5/4 (CIOMS # 8019695) were diagnosed with TB more than 90 days after the last dose of CZP and failed to meet the pre-specified inclusion criteria. Each of these patients received CZP and the majority were in the RA clinical studies program.

Across all the countries that participated in the CZP programs, the expected number of TB cases in the general population was estimated to be 2.6. However, the number of observed TB cases was 35 (14 confirmed). These incidences are equivalent to a standardized Incidence Rate (SIR) of 13.7 [95% CI: 9.5-19] overall with a SIR of 5.5 [95% CI: 3 -9.1] for confirmed cases. The global incidence rate of TB across all CZP studies was 5.46 per 100 pt-yrs or 2.18 per 100 pt-yrs for confirmed cases compared to a mean incidence of TB in the general population of 4.0 per 100

pt-yrs. See **Table s17**. The SIR in RA studies' patients was 20.5 [95% CI: 13.4-30.1]. For confirmed cases in RA studies, the confirmed RA cases, the SIR 10.2 [95%CI: 5.5-17.5].

Table s17. Incidence Rate of TB in Patients Exposed to CZP by Indication

Indication	Total exposure (pt*year)	Observed number of TB [95% CI]	Number of unique patients	Percent of unique patients with TB	Incidence Rate (100,000 pts*year) [95% CI]
BA HV	15.60	0 [0.00, 3.69]	78		0.00 [0.00, 23646.25]
CD	2286.29	8 [3.45, 15.76]	2508	0.3%	349.91 [151.07, 689.46]
PK HV	8.28	0 [0.00, 3.69]	48		0.00 [0.00, 44555.66]
PSO	97.04	1 [0.03, 5.57]	117	0.9%	1030.50 [26.09, 5741.57]
RA	3997.59	26 [16.98, 38.10]	2367	1.1%	650.39 [424.86, 952.97]
All	6404.80	35 [24.38, 48.68]	5118	0.7%	546.46 [380.63, 760.00]

Sponsor Table 5.1, page 50 of 62, Report No. RRCE07H0202, Risk of TB with CZP, Global Health Outcomes Research – Final October 11, 2007.

The distribution of TB cases by region is shown in **Table s18.** There were 2 cases of TB from low-incidence countries (United Kingdom and Germany, 1 patent, respectively) versus 21 cases of TB from high-incidence countries (Eastern Europe and Argentina, 20 cases and 1 case, respectively). There was no case of TB in CZP treated patients in North America.

Table s18. Cases of Tuberculosis in All CZP Clinical Development Programs

Number of TB Cases by Region and Indication (as of July 2007)				
	Crohn's Disease	Rheumatoid Arthritis	Psoriasis	Total
# Unique Patients	2,508	2,367	117	5,118
Total exposure (pt.[a]-yrs.)	2286.3 (2287.9[a])	3997.6 (4000.5[a])	97 (97[a])	6404.8 (6409.3[a])
North America	0	0	0	0
Western Europe	1	2	1 *	4
Eastern Europe	0	23 **	0	23
Japan	1	0	0	1
South Africa ***	5	0	0	5
Rest of the World	1	1 *	0	2
Total	8	26	1	35 (14 *)

Sponsor Table 9:1 and 9:2, page 14 and 13 of 62, Risk of TB with CZP Global Health Outcomes Research.
a. Total exposure for confirmed cases only Expsoure by Region.
* Confirmed cases.
** 12 of 23 cases from Eastern Europe were confirmed cases.
*** South Africa is shown as a separate region in this table yet is part of the Rest of the World for all other tables.

In order to understand the distribution of TB across countries in the CZP program, it is important to understand the background rates. The incidence rates for TB in the countries where CZP trials were conducted are shown in **Table s19** (data from WHO Tuberculosis Database, 2005). In the US, the overall incidence rate for TB is estimated to be 5 cases per 100,000 persons. In contrast in Eastern European countries, the incidence is a much 5 to 10-fold higher. This higher background rate of TB likely explains the higher rates seen in Eastern European patients in the CZP trials.

Table s19. Incidence of TB (2005) per 100,000 patients

United States	5
France	13
Belgium	13
Germany	7
Bulgaria	39
Estonia	43
Poland	26
Russia	119
South Africa	600

Sponsor Table 3:1, page 10 of 62, Risk of TB with CZP.

Time to Onset of TB

In the 35 cases of TB reported across the CZP programs, the median time (days) from first dose to onset of TB was 312 days (n = 35 mean = 299.9; median 312 (min. 49, max 908 days). Review of the published literature shows that the time to onset of active TB in spontaneous report cases was shorter for infliximab (43% within 90 days of treatment) than etanercept (10% within 90 days. [3, 4, 5, 6] The literature includes several hypotheses to understand why such a difference may exist. Considerations include the difference in TNF signaling (soluble vs. transmembrane), difference in level of TNF neutralization, level of cell death and apoptosis, modes of administration, and inhibition of interferon-gamma.[7, 8.]

Baseline PPD and Chest X-ray Results

There were a total of 23 patients reported with TB included in this safety database as of the clinical cut-off of 31Jan07. There were 2 patients with unknown Baseline PPD readings (Pts. # 28/606 and # 013/009), 2 patients with negative PPD readings (Pt. #114/ 019 and #221/003), 6 patients whose PPD tests were reported as zero (Pt. #056/012, #152/0007, # 901/0012, #102/0008, #089/011 and #156/0013); 8 patients whose PPD tests reported as between 1-5 mm (Pt. #14/1113, # 088/003, #154/0006, #901/0002, #111/008, #111/008, #212/011, # 122/ 0009 and #164/0005); and 5 patients whose PPD test were reported as ≥ 6 mm (Pt. #125/0006, #065/007, #110/012, #058/023 and #152/0017); 3 patients had chest X-rays that were reported as unavailable (Pt. #28/606, #901/0002 and #122/0009) while another patient was diagnosed with pulmonary fibrosis on Baseline chest X-ray (Pt. #152/0017). The remaining 19 patients reportedly had normal chest X-rays at Baseline.

In summary, the high incidence of TB in RA patients exposed to CZP indicates that treatment with this product is associated with an increased risk of TB and is also consistent with what has been observed with other TNF inhibitors. *In vivo* testing in animal models has shown that TNF inhibitor treatment appears to cause disruption of granulomas which normally compartmentalize but do not kill *Mycobacterium tuberculosis* and other granulomatous pathogens such as *Listeria monocytogenes, Histoplasma capsulatum.* [8, 9] The exact mechanism, however, is not known. The association between TNF inhibitor treatment and reactivation of TB has been incorporated into the current TNF inhibitor class labeling.

References
3. Wallis RS, Broder M, Wong J, Beenhouwer D. Granulomatous infections due to tumor necrosis factor blockade: correction. Clin Infect Dis 2004 Oct 15;39(8):1254-5.
4. Ehlers S. Why does tumor necrosis factor targeted therapy reactivate tuberculosis? J Rheumatol Suppl 2005 Mar;74:35-9.
5. Wallis RS, Broder M, Wong J, Lee A, Hoq L. Reactivation of latent granulomatous infections by infliximab. Clin Infect Dis 2005 Aug 1;41 Suppl 3:S194-8.
6. Furst DE, Wallis R, Broder M, Beenhouwer DO. Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. Semin Arthritis Rheum 2006 Dec;36(3):159-67. ADPE07C1710
7. Saliu OY, Sofer C, Stein DS, Schwander SK, Wallis RS. Tumor-necrosis-factor blockers: differential effects on mycobacterial immunity. J Infect Dis 2006 Aug 15;194(4):486-92.
8. Hamdi H, Mariette X, Godot V, Weldingh K, Hamid AM, Prejean MV. Inhibition of anti-tuberculosis T-lymphocyte function with tumor necrosis factor antagonists. Arthritis Res Ther 2006;8(4):R114.9.
9. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum 2004, Feb;50(2):372-9.

Malignancy

A total of 29 patients presenting with at least one malignancy were observed in the CZP RA studies. Twenty patients reported 20 malignancy cases of non-melanoma skin cancers. One patient (Pt. # 75225/1100, American) was diagnosed with three malignancies (e.g., 1 melanoma of skin and 2 breast cancers). The melanoma was diagnosed as the first malignancy. Eight of the 29 cases were excluded from the analyses because they were non-melanoma of skin cases. Non-melanoma of skin cancers are generally readily excised surgically and do not have bad outcomes. Therefore, the non-melanoma skin cancers were excluded from the primary analyses of malignancies. In addition, for purposes of comparing the background rates, non-melanoma skin cancers are excluded because data on these cancers are no included in the cancer databases, such as the SEER database.

Patients with malignancies diagnosed within 30 days following the first CZP injection were also excluded from this analysis (4 cases) including one PBO control patient (Patient # 122/1220015) whose symptoms began on PBO control but was diagnosed as bladder cancer after the patient had been switched to CZP.

A total of 21 malignancy cases (excluding 8 cases of non-melanoma skin cancers) that occurred in 21 patients during the CZP RA studies using the clinical database cut-off of January 31, 2007 were reviewed. All of these cases occurred in patients treated with CZP. One case of bladder cancer was reported in a PBO control patient (Pt # 122/0015) who was diagnosed 8 days after entering the study. Two patients (Pt. #35/35007 and Pt. #75225/1100) developed multiple malignancies (5 malignancy cases) during their study participation. The first patient developed lymphoma and cancer of the tonsil which were considered one malignancy because the lymphoma was diagnosed first. Another patient (Pt. #75225/1100) who developed 1 skin melanoma and 2 breast cancers was categorized for purposed of this analysis as melanoma of skin. The number of expected cases was 19.89 in the general population resulting in a SIR of

1.06 [95% CI: 0.65 to 1.61] for malignancies at all sites. Thus, the overall rate of malignancy was not increased over the expected rate in the general population.

Lymphoma was observed in 3 patients in the CZP RA studies for an SIR of 4.97 [95% CI: 1.03 to 14.54]. These results suggest an increased risk of lymphoma with CZP treatment in RA patients as compared to the general population. However, patients with RA are at increased risk of lymphoma. Studies have reported up to 23-fold increased risk of lymphoma in biologically naïve RA patients. When comparing the incidence rate per 100 patient-years for lymphoma, the calculated rate for CZP (0.09 per 100 pt-yrs) was similar to other TNF-inhibitors: infliximab (0.08 per 100 pt-yrs), adalimumab (0.08 per 100 pt-yrs) and etanercept (0.08 per 100 pt-yrs).

Time to Onset of Malignancy
The time from the first CZP dose to the onset of malignancy ranged from 44 to 1,148 days. The median time to the onset of the first malignancy (All RA patients exposed to CZP) was 259 days (n = 21, the mean (SD) = 353 (274.8).

Malignancy in PBO-Controlled CZP RA Studies
There were 12 malignancies reported in the PBO-controlled studies as described in **Table s20**. Ten of the patients, including 9 patients (0.5%) who received CZP at any dose and 1 patient (0.2%) who received PBO, experienced malignancies. These numbers do not include non-melanoma skin cancers which occurred in 2 patients (0.1%) who received receiving CZP. In the PBO controlled studies, all of the malignancies occurred in CZP exposed patients with the exception of 1 patient (Pt. # 122/1220015) whose symptoms began on PBO control but was diagnosed as bladder cancer after the patient had been switched to CZP.

Four patients with malignancy during the PBO controlled studies were observed to have had brief exposure to CZP. Two of these 4 patients received only a single dose of CZP prior to the onset of their malignancies. These patients included the following:
- Patient # 13/001 (Study 027) experienced metastases to the central nervous system. This patient was diagnosed with lung cancer 44 days following the first dose of CZP;
- Patient # 013/ 333 (Study 004) had a tongue neoplasm and received CZP less than 30 days prior to the onset of the malignancy.
- Patient # 013/014 (Study 027) was diagnosed with hepatic neoplasm 33 days following the first dose of CZP.
- Patient # 122/1220015 (Study 050) was diagnosed with bladder cancer 8 days after receiving CZP treatment. This patient was reported to have hematuria yet the bladder cancer was confirmed after the patient had received CZP.

Table s20. Malignancy in PBO-Controlled CZP RA Studies

Malignancies (excluding benign conditions) in PBO-Controlled Studies in RA				
PC #, Study #, Country Pt. Age/Sex	PT/ Verbatim	Treatment CZP or PBO	Exposure (days) from 1st, most recent dose	Outcome
Lymphomas				
035/ 007, Study 027 67y	Extranodal marginal zone B cell lymphoma (MALT lymphoma)	CZP 200 mg then 400 mg q4w	268, 2	Resolving
Gastrointestinal neoplasms				
13/ 333, Study 004 29y	Tonsil cancer/ Squamous cell carcinoma, tonsil	CZP 50 mg q4w	15, 15	Continues
062 023, Study 027 69y	Esophageal carcinoma Esophageal carcinoma	CZP 200 mg q2w + MTX	154, 0	Continues
804/ 002, Study 050 74y	Colon cancer/ Colonic carcinoma	CZP 400mg q2w + MTX	141, 0	Continues
Hepatobiliary neoplasms				
013/ 014, Study 027 64y	Hepatic neoplasm/ Liver tumor	CZP 200 mg q2w + MTX	33, 20	Death
Reproductive neoplasms				
109/ 016, Study 027 53y	Uterine cancer/ Adenocarcinoma uterine	CZP 200 mg q2w + MTX	191, 10	Resolved
603/ 005, Study 050 51y	Testis cancer/ Leydig cell tumor	CZP 200 mg q2w + MTX	170, 0	Resolved
Renal and urinary tract neoplasms				
122/ 0015, Study 050 63y	Bladder cancer/ Carcinoma of bladder	PBO + MTX	8,8	Resolved
Respiratory tract neoplasms				
12/ 329, Study 004 63y	Lung cancer/ Squamous cell ca, respirat. Infect.	CZP 50 mg q4w	44, 16	Resolved
Metastases				
113/ 001, Study 027 70y	Mets to CNS/ Brain metastases	CZP 200 mg q2w + MTX	10, 10	Unknown
Skin metastases				
001/ 010, Study 027 65y	Basal cell carcinoma/ Lumbar, suprascapular basil cell ca.	CZP 200 mg q2w + MTX	340, 5	Resolved
151/ 004, Study 027 66y	Basal cell ca. Basal cell ca of nose	CZP 200 mg q2w + MTX	301, 7	Resolved

(Revised from sponsor Table 2.7.4:44 on page 467 to468 of 973) The sponsor reports one additional patient, #151/005, in Study 027, who experienced basal cell carcinoma but is not included because the event was diagnosed on the date of the patient's first CZP dose. Source Listing 12.1:3

Exposure and Malignancy

The calculation for the duration of product exposure in the RA ISS database included the 12 weeks time period after the last dose of study medication. The exposure period for the development of malignancies in the 2,367 patients (1,790 CZP treated patients and 577 former PBO control patients) was calculated to be 3277.17 person years. (See **Table s21**.)

Table s21. Total Exposure for Malignancies in CZP RA Patients

Total Exposure for Malignancies in CZP RA Patients			
Indication	# of unique patients	Mean exposure by pt.-yrs.	Total exposure (pt-yrs.)
RA	2,367	1.385	3,277.17

Malignancies in Open Label Long-Term CZP RA Studies

The malignancies occurring in the long-term open-label studies are shown in **Table s22.** The most common malignancies during these studies occurred in the genitourinary system (Pt. #79344/1113); 2 ovarian (Pt. #21/417 and Pt. #68952/1029), 1 endometrial (Pt. #063/007),

1 uterine (Pt. #68750/1133), and 1 prostate (Pt. #53462/1037)]. Two additional patients (Pt. # 011/ 320 and Pt. #51695/1117) developed lymphomas during the OL studies.

Table s22. Malignancies in Open-Label CZP RA Studies

Malignancies (excluding benign conditions) in Open-Label CZP Studies in RA				
Pt. #, Study #, Country Pt. Age/Sex	PT/ Verbatim	Treatment CZP or PBO	Exposure (days) from 1st, most recent dose	Outcome
Lymphomas				
011/ 320, Study 004 66y/	Non-Hodgkins lymphoma/ Follicle-derived lymphoma	CZP 200 mg then 400 mg q4w	159, 21	Continues
51695/ 1117, Study 015 59y	Diffuse large B-cell lymphoma/ same	CZP 400 mg q4w	682, 38	Continues
Endocrine neoplasms				
20833/ 1238, Study 015 62y	Thyroid gland cancer/ Thyroid carcinoma	CZP 400 mg q4w + MTX	242, 8	Resolving
Gastrointestinal neoplasms				
51695/ 1117, Study 015	Tonsil cancer/ Squamous cell ca. of tonsil	CZP 400 mg q4w	669, 25	Continues
056/ 004, Study 028 60y	Malignant peritoneal neoplasm/ Carcinoma of retroperitoneum	CZP 400 mg q2w + MTX	116, 3	Unknown
Breast neoplasms				
75225/ 1101, Study 015 55 y	Breast cancer/ Invasive poorly differentiated ductal adenoca.	CZP 400 mg q4w + MTX	519, 15	Resolved with sequelae
75225/ 1162, Study 015 69y	Breast cancer Stage-I /Ductal ca. left breast, Grade 1.	CZP 400 mg q4w + MTX	1148, 1	Resolved
Renal and urinary tract neoplasms				
79344/ 1113, Study 015 77y	Renal cell carcinoma/ Renal cell carcinoma, left	CZP 400 mg q4w + MTX	679, 11	Resolved
Reproductive neoplasms				
21/ 417, Study 004 59y	Ovarian cancer/ same	CZP 200 mg then 400 mg q4w	121, 37	Continues
68952/ 1029, Study 015 71y	Ovarian cancer/ Ovarian carcinoma	CZP 400 mg q4w + MTX	412, 41	Resolved
68750/ 1133, Study 015 48y	Uterine cancer/ Adenocarcinoma uterine ca.	CZP 400 mg q4w + MTX	405, 26	Resolved
063/ 007, Study 028 63y	Endometrial cancer/ Adenocarcinoma endometrial	CZP 400 mg q2w + MTX	427, 22	Continues
53462/ 1037, Study 015 69y	Prostate cancer/ same	CZP 400mg q4w	259, 11	Unknown
Skin neoplasms				
75225/ 1100, Study 015 53y	Basal cell carcinoma/ Squamous cell ca. forehead Malignant melanoma in situ, left scapular area	CZP 400 mg q4w + MTX	352, 16	Resolved
151/ 004, Study 028 67y	Basal cell carcinoma/ Basal cell carcinoma of nose	CZP 400 mg q2w + MTX	301, 7	Resolved
148/ 0020, Study 028 75y	Basal cell carcinoma/ Basal carcinoma of nose	CZP 400 mg q2w + MTX	372, 8	Resolved
Respiratory tract neoplasms				
56478/ 1175, Study 015 60y	Lung cancer metastatic/ Pulmonary neoplasm	CZP 400 mg q4w	767, 7	Death
500/ 0001, Study 051 58y	Lung cancer metastatic/ Carcinoma right lung	CZP 200 mg q2w + MTX	168, 0	Resolved with sequelae

Revised from sponsor Table 2.7.4:45, page 471 – 473 of 973; Source Listing 12.1:3, Global Drug Safety Database

The incidence rate of malignancy (PBO-controlled studies) across all indications is shown in **Table s23.** The RA population had the highest incidence of observed malignancies, 0.90 [95% CI: 0.41, 1.71] compared with Crohn's Disease and psoriasis.

Table s23. Incidence Rate of Malignancies in PBO-Controlled Across All Indications

Incidence Rate of Malignancies in PBO-Controlled Studies Only (excluding non-melanoma skin cancer)					
Indication	Total Exposure (pt.-yrs.)	Observed # Events [95% CI]	# unique patients	% unique patients with events	Incidence rate (100 pts.-yrs.) [95% CI]
Crohn's disease	302.95	1 [0.03, 5.57]	834	0.10%	
Psoriasis	64.47	0	117		0
RA	998.89	9 [4.32, 17.08]	1774	0.50%	0.90 [0.41, 1.71]
All Programs	1366.31	10 [4.80, 18.39]	2725	0.40%	0.73 [0.35, 1.35]

Cancer Databases

The SIR for malignancies (excluding non-melanoma skin cancer) in the CZP RA studies was calculated by comparing the incidence rates of malignancies observed during clinical trials to the incidence rates reported by the World Health Organization Global Cancer (WHO GLOBOCAN) database and the Surveillance Epidemiology and End Results (SEER) database from the National Cancer Institute.

The WHO GLOBOCAN database provided incidence rates of malignancies by country as well as controls and adjusted for age and gender. The SEER database (US-based database) does not accurately reflect or control for the countries where many CZP studies were conducted. In view of this concern, the GLOBOCAN database better reflects the patients in the CZOP RA studies global program. For purposes of this safety database analysis, malignancies were attributed to CZP if the patient received at least 1 dose of CZP for RA.

There were 19.89 expected malignancy cases based on the (GLOBOCAN database and 23.94 expected cases based on the SEER database) compared to a total of 21 observed malignancy cases in the RA safety database. There was a higher than expected number of lymphoma cases (3 cases versus 0.60 cases in the GLOBOCAN and 0.97 cases in SEER). See **Tables s24** and **s25.**

As mentioned above, a total of three cases of lymphoma were observed in the CZP RA studies. The number of expected lymphoma cases was 0.60 compared with 3 observed lymphoma cases yielding a SIR for lymphoma of 4.97 [95%CI: 1.03 to 14.54] using the GLOBOCAN database. All 3 lymphoma patients were between 57 and 67 years of age and were female. One of these cases with non-Hodgkin's lymphoma (NHL) had a MALT lymphoma which is known to be associated with autoimmune disorders.

In summary, these data suggest that there does not appear to be increased risk of developing a malignancy in patients treated with CZP. Compared to other TNF inhibitors and as confirmed by the GLOBOCAN malignancy database (which accounts for global epidemiology malignancy data), this outcome is consistent with what has been observed with other TNF inhibitors.

The CZP RA data suggests that there may be an increased risk of lymphoma with CZP treatment. However, this conclusion is uncertain because of the increased background risk of lymphoma in patients with RA. In general, these data are consistent with what has been seen with other TNF inhibitors. The current labeling for TNF-inhibitors reflects Malignancy/Lymphoproliferative Diseases information in WARNINGS, PRECAUTIONS and ADVERSE REACTIONS sections.

Table s24. GLOBOCAN and SEER SIR – Malignancy by Type in CZP RA Studies

Cancer Type	Observed	Expected		SIR		95% CI	
		GLOBO	SEER	GLOBO	SEER	GLOBO	SEER
All Sites	21	19.89	23.94	1.06	0.88	0.65-1.61	0.54-1.34
Breast	2	4.28	6.23	0.47	0.32	0.06-1.69	0.04-1.16
Colorectal	1	2.49	2.26	0.40	0.44	0.01-2.23	0.01-2.47
Lung	3	2.20	3.11	1.36	0.96	0.28-3.98	0.20-2.82
Lymphoma	3	0.60	0.97	4.97	3.10	1.03-14.54	0.64-9.05
Melanoma	1	0.57	0.88	1.75	1.13	0.04-9.75	0.03-6.31
Prostate	1	1.09	2.18	0.91	0.46	0.02-5.08	0.01-2.56
Uterine	2	1.02	1.19	1.96	1.68	0.24-7.07	0.20-6.06

Note: CI=confidence Interval; GLOBO=GLOBOCAN; SIR-standardized incidence ratio. Source Table 2.7.4:46. Sponsor Table 11.7, page 32 of 38

Table s25. Incidence of Lymphomas in Clinical Studies RA Population

Incidence of Lymphoma in Clinical Studies in RA Population				
Parameter	Enbrel Etanercept	Remicade Infliximab	Humira Adalimumab	CIMZIA certoluzimab pegol
# Cases / # of Patients	9 cases / 5,723	2 cases / na	10 cases / 2,468	3 cases / 2,367 RA
Incidence (Cases/ pt-yrs)	9 cases / 11,201	N/A	10 cases "over 13,000"	3 cases / 3,277 RA
Incidence rates per 100 pt -yrs 100 pt.yrs [95%CI]	0.08 [95%CI: n/a]	0.08 [95%CI: n/a]	0.08 [95%CI: n/a]	0.09 [95%CI: 0.02 - 0.27]
Data source	Label Insert 2006	Label Insert Apr-07	Label Insert Feb-07	BLA 125271 CZP in RA

Revised from sponsor Table 7:1, page 19 of 38

Serious Hepatic Events and Other Hepatic Events of Interest

In the PBO controlled studies in the Hepatobiliary Disorders (SOC), a higher percentage of patients in the All CZP Doses group versus PBO control experienced SAEs (0.4% versus 0%). The most common Hepatic SAEs observed were HLT Cholecystitis and Cholelithiasis, All CZP Doses group (0.6%) versus PBO-control (0%).

In the PBO controlled studies, the primary SOC Investigations TEAEs observed were 16% in All CZP Doses group versus 11.5% in the PBO control group. Among CZP dose regimens, more Investigations TEAEs were observed (18%) in CZP 400 mg q2w compared to (15%) in CZP 200 mg q2w group and (13%) in CZP 400 mg q4w group.

Hepatic events of special interest were the following: one patient (Pt. # 023/001) developed hepatic cirrhosis and died. Her narrative is in Section 7.3.1 Deaths of this review. One patient (Pt. # 027/039) was a 49 year old female (Study 004) diagnosed with autoimmune hepatitis after a total of 24 weeks CZP exposure (CZP 400 mg in Study 004 followed by CZP 200 mg q4w).

Concomitant medications at the time of the event were not available. Hepatic enzymes were elevated (AST 42-65 U/L; ALT 64-114 U/L; GGT 35-52 U/L) and she was subsequently withdrawn from the study. Her liver function analyses returned to normal and she was diagnosed with autoimmune hepatitis. Causality could not be determined as related to the study product. Patient # 011/014 was a 50 year old female who subsequently developed Grade 4 transaminase elevations and was diagnosed with hepatic neoplasm. Her narrative is in Section 7.3.1 Deaths of this review.

Liver Function Tests
Examination of the rates of hepatobiliary TEAEs and liver enzyme elevations did not indicate a higher rate of TEAEs among CZP treated patients.

Elevated Bilirubin
A total of 5 patients observed with elevated bilirubin were in the All CZP Doses group versus no patients in the PBO control group. There were no SAEs or AEs leading to withdrawal due to hyperbilirubinemia. Only one patient (Pt. # 1849/1087), a 52-year old male (PBO control group in Study 014 who received CZP 400 mg q4w in Study 015) was observed with elevated bilirubin (87 µmol/L, elevated GGT 223 IU/L and normal AST and ALT (33 and 37 IU/L, respectively). Concomitant medications included MTX and salbutamol. Follow-up bilirubin tests were normal. There were no other associated AEs of elevated bilirubin.

Overall in this safety database, no clinically significant hepatotoxicity was observed in the CZP treated population. The current CIMZIA® labeling in the WARNINGS AND PRECAUTIONS includes a subsection, Hepatitis B Virus Reactivation, as well as in the ADVERSE REACTIONS, (b) (4)

Bleeding Events
During review of the CZP submission for Crohn's disease there were concerns about bleeding events in view of reports of abnormalities in coagulation tests. These abnormalities were ultimately attributed to interference of CZP in the blood with the coagulation assays. Nonetheless, to address the possibility of increased bleeding events, we examined an analysis of all treatment emergent bleeding events. **Table s26** presents events analyzed as the percent of patients and the exposure-adjusted rate (events per 100 pt-yrs). The analysis showed no increase in the exposure adjusted rate of bleeding events overall (11.67 per 100 pt-yrs) with CZP versus 11.75 per 100 pt-yrs with PBO). Examining the rates for individual types of bleeding events, the exposure adjusted rates were not higher with CZP than PBO with the exception of injection site bruising (2.74 versus 1.23 per 100 pt-yrs), dysfunctional uterine bleeding (1.61 versus 1.23 per 100 pt-yrs and ecchymoses (1.92 versus 0.82 per 100 pt-yrs). The higher rates of injection site bruising and ecchymoses suggest local effects of the CZP injection and not systemic effects for the risk of bleeding. Regarding the risk of dysfunctional uterine bleeding, the risk decreased during long-term treatment to a rate that was lower than that seen with PBO in controlled portions of the studies. Thus, these data do not confirm a safety sign. In summary, these data do not indicate an increased risk of bleeding with CZP.

Table s26. Treatment Emergent Bleeding Events – PBO-Controlled and All Studies CZP in RA

Treatment Emergent Bleeding Events - PBO-controlled and All Studies CZP in RA Reported numbers are from the Amendment 5, submitted May 30, 2008						
Combined Term	PBO N=647		All CZP Doses (PBO-controlled) N=1774		All CZP Doses (All Studies) N=2367	
	n (%)	100 p-y	n (%)	100 p-y	n (%)	100 p-y
Total # of Pts. with Bleeding Events	28 (4.3%)	11.75	111 (6.3%)	11.67	190 (8%)	6.2
Blood urine	10 (1.5%)	4.12	25 (1.4%)	2.53	43 (1.8%)	1.32
Injection site bruising	3 (0.5%)	1.23	27 (1.5%)	2.74	39 (1.6%)	1.21
Dysfunctional uterine bleeding	3 (0.5%)	1.23	16 (0.9%)	1.61	34 (1.4%)	1.05
Ecchymoses	2 (0.3%)	0.82	18 (1.0%)	1.92	3 (1.4%)	1.05
Gastrointestinal hemorrhage	3 (0.5%)	1.23	12 (0.7%)	1.2	18 (0.8%)	0.55
Conjunctival hemorrhage	1 (0.2%)	0.41	2 (0.1%)	0.2	5 (0.2%)	0.15
Other hemorrhage	7 (1.1%)	2.87	13 (0.7%)	1.3	35 (1.5%)	1.08
Purpura	1 90.2%)	0.41	2 (0.1%)	0.2	4 (0.2%)	0.12
Hemorrhage male	0	0	1 (0.1%)	0.1	1 (0.0%)	0.03

Sponsor Table 10:19, page 41 of 47, Amendment 5 submitted May 30, 2008 to this BLA.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common Adverse Events in the PBO-controlled CZP RA Trials

In the PBO-controlled trials, a higher percentage of patients in the All CZP Doses group (79%) experienced common AEs (≥ 0.5%) versus the PBO group (62%). When the incidence of the AEs were corrected for duration of exposure, per Amendment 5 submitted to the BLA on May 30, 2008, the rate was 323 cases per 100 pt-yrs for the PBO-control compared to 239 cases per 100 pt-yrs in CZP 200 mg q2w group, 266 cases per 100 pt-yrs in CZP 400 mg q2w group, 654 cases per 100 pt-yrs in CZP 400 mg q4w group and 285 cases per 100 pt-yrs in the All CZP Doses group. These data do not indicate a clear dose response for adverse events but they do indicate that the trial that explored the 400 mg q4w dosing had a high rate of adverse events.

In the PBO-controlled trials, the most common TEAEs observed were Infections and Infestations, (38% All CZP Doses group compared with 23% the PBO-control group) followed by Musculoskeletal and Connective Tissue Disorders (18% versus 19%); GI Disorders (16% versus 14%); General Disorders and Administration Site Conditions (15% versus 17%); Investigations (15% versus 10%); Skin and Subcutaneous Tissue Disorders (13% versus 6%); and Nervous System Disorders (12% versus 12%) (All CZP Doses group compared with the PBO control group). See **Tables s27-a, s27-b** and **s27-c.**

In the PBO controlled studies, AEs ≥ 3% are shown in **Table s27-d** and **s27-e.** The most common TEAES that occurred at a higher percentage in the All CZP Doses group compared to PBO control were: Upper respiratory tract infections (18% versus 9%), lower respiratory tract and lung infections (6% versus 3%) and bacterial infections (3% versus 1.7%) All CZP Doses group compared to PBO control patients, respectively.

More TEAEs were observed in the category of skin and subcutaneous tissue disorders with CZP than with PBO (13% versus 6%). The higher rate is accounted for by an increased rate of rash (3% versus 1.5%), allergic dermatitis (0.7% versus 0%), pruritus (1.5% versus 0.5%) urticaria (0.9% versus 0.3%) and alopecia (1% versus 0.2%).

Table s27-a. Common AEs in ≥ 0.5% in PBO-Controlled CZP RA Trials

Common AEs ≥0.5% for All SOC/HLT/PT in PBO-Controlled Studies in RA					
Primary SOC, PT	PBO N=647	CZP 200 mg [W] q2w N = 640	CZP 400 mg q2w N = 635	CZP 400 mg q4w N = 278	All CZP Doses N = 1774
Total Exp. Pt.-Yrs.	225	396	410	166	957
Total AEs (# Pts. w AE, % pts)	1372 (404, 62%)	1852 (433, 68%)	1859 (425, 67%)	812 (216, 78%)	5331 (1258, 71%)
Blood: lymphatic disorders	24 (3.7%)	53 (8%)	43 (7%)	6 (2.2%)	110 (6.2%)
Eosinophilia	3 (0.3%)	17 (2.7%)	13 (2.0%)	0	30 (1.7%)
Anemia	8 (1.2%)	11 (1.7%)	11 (1.7%)	2 (0.7%)	24 (1.4%)
Cardiac disorders	13 (2%)	19 (3%)	22 (3.5%)	9 (3.2%)	60 (3.4%)
Tachycardia	0	5 (0.8%)	3 (0.5%)	1 (0.4%)	9 (0.5%)
Supraventricular arrhythmias	3 (0.5%)	6 (0.9%)	2 (0.3%)	1 (0.4%)	11 (0.6%)
Ischmeic coronary artery dis.	2 (0.3%)	4 (0.6%)	4 (0.6%)	3 (1.1%)	13 (0.7%)
Palpitations	4 (0.6%)	2 (0.3%)	2 (0.2%)	3 (1.1%)	9 (0.5%)
Ear (labyrinth disorders	5 (0.8%)	9 (1.4%)	9 (1.4%)	5 (1.8%)	26 (1.5%)
Vertigo	2 (0.3%)	3 (0.6%)	9 (1.4%)	4 (1.4%)	17 (1.0%)
Endocrine disorders	1 (0.2%)	5 (0.8%)	4 (0.6%)	0	11 (0.6%)
Eye disorders	15 (2%)	20 (3.1%)	33 (5.2%)	7 (2.5%)	69 (3.9%)
Conjunctivitis/ Infections	3 (0.5%)	8 (1.3%)	12 (1.9%)	2 (0.7%)	25 (1.4%)
Cataract	2 (0.3%)	5 (0.8%)	6 (0.9%)	0	11 (0.6%)
Gastrointestinal disorders	88 (13.6%)	85 (13.3%)	81 (12.8%)	57 (20.5%)	276 (15.6%)
Abdominal pain upper	8 (1.2%)	11 (1.7%)	4 (0.6%)	4 (1.4%)	25 (1.4%)
Abdominal pain	3 (0.5%)	8 (1.3%)	12 (1.9%)	3 (1.1%)	24 (1.4%)
Vomiting	10 (1.5%)	11 (1.7%)	3 (0.5%)	6 (2.2%)	25 (1.4%)
Nausea	20 (3.1%)	9 (1.4%)	14 (2.2%)	7 (2.5%)	45 (2.5%)
Dyspepsia	14 (2.2%)	15 (2.3%)	10 (1.6%)	8 (2.9%)	39 (2.3%)
Toothache	3 (0.5%)	10 (1.6%)	10 (1.6%)	0	22 (1.2%)
Diarrhea	18 (2.8%)	10 (1.6%)	90 (1.4%)	21 (5.8%)	55 (2.5%)
Gastritis	1 (0.2%)	9 (1.4%)	12 (1.9%)	2 (0.7%)	23 (1.4%)
GI reflux disease	1 (0.2%)	4 (0.6%)	3 (0.5%)	2 (0.7%)	11 (0.6%)
Constipation	8 (1.2%)	2 (0.3%)	6 (0.8%)	4 (1.1%)	20 (1.0%)
Mouth ulceration	3 (0.5%)	8 (0.9%)	2 (0.3%)	0	14 (0.6%)
GI dis. Flatulence, bloat, disten.	5 (0.3%)	1 (0.2%)	3 (0.5%)	2 (0.7%)	9 (0.5%)
General dis. site administration	179 (110, 17%)	169 (97, 15.2%)	151 (78, 12.3%)	79 (47, 17%)	451 (272, 15.3%)
Injection & infusion site. reactions	81 (6.5%)	70 (6.6%)	74 (5.8%)	30 (6.1%)	213 (6.4%)
Injection site reaction	8 (1.1%)	11 (1.4%)	4 (0.6%)	9 (1.8%)	40 (1.5%)
Injection site hematoma	0	12 (1.3%)	16 (0.9%)	0	28 (0.8%)
Injection site pain	33 (2.5%)	8 (1.3%)	8 (0.9%)	7 (1.8%)	37 (1.5%)
Injection site discoloration	0	19 (1.1%)	13 (1.4%)	0	32 (0.9%)
Injection site erythema	12 (1.1%)	9 (1.1%)	20 (1.1%)	6 (1.0%)	41 (1.2%)
Injection site bruising	2 (0.3%)	2 (0.3%)	5 (0.5%)	5 (1.1%)	13 (0.5%)
Injection site rash	1 (0.2%)	2 (0.3%)	5 (0.5%)	2 (0.7%)	9 (0.4%)
Injection site irritation	16 (1.7%)	1 (0.2%)	0	1 (0.4%)	2 (0.1%)
Asthenic conditions	32 (4.2%)	38 (4.1%)	21 (3%)	24 (6.5%)	97 (4.3%)
Fatigue	27 (3.4%)	26 (3%)	13 (1.9%)	22 (5.8%)	69 (3.1%)
Asthenia	5 (0.8%)	5 (0.8%)	8 (1.1%)	1 (0.4%)	18 (1.0%)
Pyrexia	14 (1.7%)	29 (3.3%)	26 (2.8%)	5 (1.8%)	67 (2.8%)
Edema NEC	19 (2.2%)	10 (1.4%)	14 (1.6%)	1 (0.4%)	32 (1.4%)
Peripheral edema	15 (1.7%)	10 (1.4%)	14 (1.6%)	1 (0.4%)	29 (1.3%)
Pain, discomfort NEC	13 (1.7%)	7 (1.1%)	4 (0.6%)	11 (3.2%)	31 (1.6%)
Chest pain	8 (1.2%)	5 (0.8%)	3 (0.5%)	6 (1.8%)	19 (1.0%)
Pain	3 (0.3%)	1 (0.2%)	1 (0.2%)	4 (1.4%)	10 (0.5%)
General sx, sy NEC	12 (1.5%)	7 (0.6%)	4 (0.6%)	6 (2.2%)	25 (1.2%)
Influenze like illness	5 (0.8%)	3 (0.3%)	1 (0.2%)	5 (1.8%)	12 (0.6%)
Chills	4 (0.6%)	5 (0.5%)	5 (0.8%)	0	13 (0.6%)
Hepatobiliary disorders	8 (7, 1.1%)	23 (16, 2.5%)	15 (11, 1.7%)	2 (2, 0.7%)	41 (30, 1.7%)
Cholelithiasis	2 (0.3%)	9 (0.9%)	6 (0.6%)	0	15 0.6%)
Liver disorder	1 (0.2%)	7 (0.6%)	4 (0.6%)	0	11 (0.5%)
Hepatocellular damage, hepatitis NEC	3 (0.3%)	2 (0.3%)	1 (0.2%)	2 (0.7%)	6 (0.3%)
Immune system disorders	4 (4, 0.6%)	6 (5, 0.8%)	7 (6, 0.9%)	5 (5, 1.8%)	24 (20, 1.1%)

Source Table 8.1:10, pages 89 to 296 of 13,991. Adverse events are displayed as #AEs (#Pts, % Pts.). A patient experiencing more than one AE in a category is counted only once in that category.

Table s27-b. Common AEs in ≥ 0.5% in PBO-Controlled CZP RA Trials

Common AEs ≥ 0.5% for All SOC/HLT/PT in PBO-Controlled Studies in RA					
Primary SOC, PT	PBO N=647	CZP 200 mg (a) q2w N = 640	CZP 400 mg q2w N = 635	CZP 400 mg q4w N = 278	All CZP Doses N = 1774
Total Exp. Pt.-Yrs.	225	396	410	106	957
Total # AEs (# Pts. w/ AE, %)	1372 (404, 63%)	1852 (433, 68%)	1859 (425, 67%)	812 (216, 78%)	5331 (1258, 79%)
Infections, infestations	232 (148, 22.9)	443 (239, 37.3%)	437 (239, 37.6%)	141 (103, 37.1%)	1,146 (667, 37.6%)
Upper respirat.tract infections	74 (9.4%)	152 (16.7%)	142 (15.9%)	66 (19.8%)	418 (17.6%)
UR tract infection	21 (2.8%)	41 (5.5%)	31 (3.9%)	18 (6.1%)	103 (5%)
Nasopharyngitis	27 (3.4%)	43 (4.5%)	43 (5.4%)	25 (8.3%)	135 (6.1%)
Pharyngitis	5 (0.8%)	21 (3.1%)	18 (2.5%)	2 (0.7%)	46 (2.4%)
Sinusitis	9 (1.4%)	17 (2.2%)	11 (1.6%)	13 (3.6%)	44 (2.1%)
Rhinitis	4 (0.6%)	15 (2.0%)	11 (1.7%)	3 (1.1%)	41 (2.1%)
Tonsillitis	1 (0.2%)	8 (1.1%)	8 (1.3%)	2 (0.7%)	19 (1.0%)
Urinary tract infec.	39 (4.5%)	48 (6.3%)	63 (7.2%)	6 (2.2%)	132 (5.8%)
Urinary tract infection	35 (4.0%)	40 (5.2%)	55 (6.0%)	4 (1.4%)	112 (4.7%)
Lower respir. tract, lung infect.	25 (3.4%)	39 (5.8%)	39 (5.8%)	19 (5.0%)	112 (5.6%)
Bronchitis acute	5 (0.6%)	20 (3.0%)	23 (3.5%)	2 (0.4%)	49 (2.5%)
Bronchitis	13 (1.7%)	10 (1.4%)	7 (1.1%)	11 (3.2%)	31 (1.6%)
Pneumonia	3 (0.5%)	5 (0.8%)	7 (1.1%)	1 (0.4%)	14 (0.8%)
Lower respir. tr. infection	4 (0.6%)	0	0	4 (1.1%)	11 (0.5%)
Bacterial infections NEC	11 (1.7%)	26 (4.1%)	29 (4.6%)	3 (0.4%)	73 (3.3%)
Bacteriuria	8 (1.1%)	16 (2.2%)	20 (2.5%)	0	37 (1.7%)
Cellulitis	1 (0.2%)	3 (0.5%)	5 (0.8%)	3 (0.4%)	14 (0.6%)
Viral infec. NEC	10 (1.2%)	27 (3.9%)	21 (3.0%)	2 (0.7%)	51 (2.6%)
Respiratory tr. infect. viral	3 (0.3%)	11 (1.6%)	7 (0.8%)	0	18 (0.8%)
Viral infection	0	9 (1.4%)	7 (1.1%)	1 (0.4%)	17 (1.0%)
Herpes viral infections	9 (1.2%)	32 (3.1%)	35 (4.1%)	10 (3.6%)	84 (3.6%)
Herpes simplex	5 (0.8%)	27 (2.5%)	27 (2.8%)	9 (3.2%)	70 (2.8%)
Herpes zoster	3 (0.3%)	5 (0.8%)	6 (0.9%)	1 (0.4%)	12 (0.7%)
Infections NEC	9 (0.9%)	23 (3.0%)	15 (2.0%)	3 (1.1%)	44 (2.1%)
Respiratory tr. infection	1 (0.2%)	18 (2.3%)	8 (1.1%)	1 (0.4%)	28 (1.4%)
Localized infection	0	2 (0.3%)	2 (0.3%)	2 (0.7%)	8 (0.5%)
Influenza viral infections	9 (1.4%)	20 (2.8%)	6 (0.9%)	6 (2.2%)	34 (1.8%)
Influenza	9 (1.2%)	20 (2.8%)	6 (0.9%)	6 (2.2%)	34 (1.8%)
Skin, soft tissue infections	9 (1.2%)	13 (1.7%)	19 (1.9%)	3 (1.1%)	37 (1.6%)
Ear infections	2 (0.3%)	11 (1.4%)	1 (0.2%)	1 (0.4%)	16 (0.8%)
Dental, oral soft tiss. infections	12 (1.2%)	8 (1.3%)	11 (1.6%)	3 (1.1%)	23 (1.2%)
Abdominal, GI infections	4 (0.6%)	6 (0.9%)	5 (0.8%)	5 (1.4%)	19 (1.0%)
Fungal infections NEC	4 (0.5%)	9 (0.9%)	6 (0.8%)	4 (1.4%)	21 (1.0%)
Tuberculosis infections	0	5 (0.8%)	4 (0.6%)	0	9 (0.5%)
Disseminated tuberculosis	0	3 (0.5%)	1 (0.2%)	0	4 (0.2%)
Candida infections,	3 (0.5%)	4 (0.6%)	4 (0.5%)	2 (0.7%)	11 (0.6%)
Streptococcal infections	1 (0.2%)	2 (0.3%)	7 (1.1%)	1 (0.4%)	10 (0.6%)
Injury, poisoning, procedural complications	48 (34, 5.3%)	77 (53, 8.3%)	85 (58, 9.1%)	21 (19, 6.8%)	199 (145, 8.2%)
Non-site specific injuries NEC	13 (1.7%)	17 (2.3%)	16 (2.2%)	7 (2.5%)	44 (2.3%)
Fall	1 (0.2%)	4 (0.5%)	4 (0.6%)	3 (1.1%)	12 (0.6%)
Limb injuries NEC	6 (0.8%)	10 (1.4%)	12 (1.7%)	2 (0.7%)	26 (1.3%)
Skin injuries NEC	4 (0.6%)	13 (1.4%)	20 (2.4%)	3 (1.1%)	41 (1.8%)
Contusion	3 (0.5%)	6 (0.9%)	15 (1.7%)	2 (0.7%)	26 (1.2%)
Lower limb fractures, dislocations	2 (0.3%)	3 (0.5%)	7 (1.1%)	1 (0.4%)	12 (0.7%)
Upper limb fractures, dislocations	4 (0.3%)	5 (0.8%)	8 (1.1%)	1 (0.4%)	14 (0.7%)

Source Table 8.1:10, pages 89 to 296 of 13,991. Adverse events are displayed as #AEs (#Pts, % Pts.). A patient experiencing more than one AE in a category is counted only once in that category.

Table s27-c. Common AEs in ≥ 0.5% in PBO-Controlled CZP RA Trials

Common AEs > 0.5% for All SOC/HLT/PT in PBO-Controlled Studies in RA					
Primary SOC, PT	PBO N=647	CZP 200 mg (a) q2w N = 640	CZP 400 mg q2w N = 635	CZP 400 mg q4w N = 278	All CZP Doses N = 1774
Total Exp. Pt.-Yrs.	225	396	410	106	957
Total # AEs (# Pts. w/ AE, %)	1372 (404, 63%)	1852 (433, 68%)	1859 (425, 67%)	812 (216, 78%)	5331 (1258, 79%)
Investigations	120 (66, 10.2%)	172 (97, 15.2%)	193 (112, 17.6%)	62 (34, 12.2%)	473 (272, 15.3%)
Liver function analyses	61 (4.8%)	73 (6.9%)	86 (8.5%)	22 (4.3%)	197 (6.7%)
Hepatic enzyme increased	11 (1.2%)	21 (2.2%)	21 (2.5%)	1 (0.4%)	43 (1.7%)
Alanine aminotransfer. increased	20 (2.3%)	15 (2.0%)	24 (3.1%)	8 (2.5%)	55 (2.6%)
Aspartate aminotransfer. increased	12 (1.9%)	12 (1.6%)	18 (2.2%)	4 (1.4%)	40 (1.9%)
GGT increased	12 (1.4%)	14 (1.6%)	8 (1.1%)	7 (1.8%)	30 (1.3%)
Transaminases increased	5 (0.6%)	5 (0.6%)	12 (1.9%)	1 (0.4%)	18 (1.0%)
Blood bilirubin increasaed	0	4 (0.5%)	2 (0.3%)	0	6 (0.3%)
Coagulation, bleeding analyses	3 (0.5%)	21 (2.0%)	18 (1.9%)	4 (0.4%)	43 (1.5%)
aPTT prolonged	2 (0.3%)	13 (1.9%)	14 (1.9%)	1 (0.4%)	28 (1.4%)
White blood cells analyses	9 (0.8%)	16 (1.9%)	16 (1.3%)	1 (0.4%)	39 (1.5%)
Physical exam. Procedures	4 (0.5%)	10 (1.4%)	9 (0.8%)	5 (1.8%)	26 (1.2%)
Autoimmunity procedures	1 (0.2%)	10 (1.1%)	3 (0.5%)	3 (1.1%)	16 (0.7%)
Anti-nuclear antibody	1 (0.2%)	5 (0.8%)	2 (0.3%)	2 (0.7%)	9 (0.5%)
Renal function analyses	3 (0.3%)	4 (0.5%)	5 (0.6%)	2 (0.7%)	15 (0.6%)
Blood creatinine increased	1 (0.2%)	2 (0.3%)	4 (0.6%)	1 (0.4%)	11 (0.5%)
Urinalysis NEC	6 (0.8%)	5 (0.5%)	7 (1.1%)	1 (0.4%)	14 (0.7%)
Vascular tests NEC (including BP)	3 (0.5%)	4 (0.5%)	8 (0.9%)	2 (0.7%)	15 (0.7%)
BP increased	3 (0.5%)	3 (0.5%)	8 (0.9%)	2 (0.7%)	14 (0.7%)
Skeletal, cardiac muscle analyses	3 (0.5%)	2 (0.3%)	12 (1.9%)	8 (1.4%)	22 (1.0%)
Blood CPK increased	3 (0.5%)	2 (0.3%)	12 (1.9%)	8 (1.4%)	22 (1.0%)
Metabolism, nutrition disorders	7 (7, 1.1%)	22 (14, 2.2%)	20 (15, 2.4%)	7 (6, 2.2%)	59 (45, 2.5%)
Musculoskeletal, connective tissue disorders	191 (121, 18.7%)	188 (104, 16.3%)	179 (97, 15.3%)	83 (51, 18.3%)	594 (326, 18.4%)
Musculoskeletal and CT sx,sy NEC	39 (4.2%)	55 (5.9%)	55 (6.5%)	25 (7.6%)	159 (6.7%)
Back pain	11 (1.1%)	25 (3.6%)	31 (4.3%)	11 (3.2%)	74 (3.7%)
Pain in extremity	10 (1.2%)	9 (1.3%)	8 (0.9%)	8 (2.5%)	30 (1.4%)
Rheumatoid arthritis	70 (8.0%)	33 (3.9%)	28 (3.6%)	12 (3.2%)	117 (4.9%)
Arthralgia	19 (2.5%)	18 (2.5%)	7 (1.1%)	8 (2.2%)	50 (2.3%)
Joint swelling	10 (1.2%)	5 (0.8%)	3 (0.5%)	5 (1.4%)	22 (1.0%)
Muscle pains	10 (1.2%)	8 (0.9%)	9 (0.9%)	2 (0.7%)	26 (1.1%)
Arthropathies NEC	6 (0.9%)	6 (0.8%)	3 (0.5%)	4 (1.4%)	22 (1.1%)
Muscle related signs, symptoms NEC	5 (0.8%)	5 (0.8%)	15 (1.6%)	6 (1.8%)	32 (1.4%)
Synovial disorders	6 (0.8%)	1 (0.2%)	13 (1.6%)	2 (0.7%)	34 (1.2%)
Neoplasms benign, malignant, unspecified	8 (6, 0.9%)	17 (12, 1.9%)	12 (9, 1.4%)	3 (2, 0.7%)	37 (28, 1.6%)
Nervous system disorders	112 (76, 11.7%)	88 (56, 8.8%)	93 (61, 9.6%)	96 (61, 21.9%)	341 (218, 12.3%)
Headaches	50 (6.0%)	44 (4.8%)	38 (4.1%)	41 (12.2%)	164 (6.7%)
Paraesthesias and dysaesthesia	14 (1.7%)	14 (1.6%)	12 (1.7%)	21 (5.0%)	55 (2.2%)
Hypoesthesia	5 (0.5%)	7 (0.8%)	4 (0.6%)	7 (1.4%)	21 (0.8%)
Paraesthesias	8 (1.1%)	7 (0.8%)	6 (0.8%)	9 (2.5%)	27 (1.1%)
Dizziness	15 (1.9%)	5 (0.8%)	10 (1.4%)	11 (3.2%)	34 (1.7%)
Disturbance of consciousness NEC	10 (1.4%)	5 (0.6%)	9 (1.3%)	6 (1.4%)	23 (1.0%)
Psychiatric disorders	41 (4.2%)	25 (3.1%)	23 (2.8%)	13 (4.3%)	75 (3.6%)
Renal and urinary disorders	31 (16, 2.5%)	41 (30, 4.7%)	50 (29, 4.6%)	16 (10, 3.6%)	120 (82, 4.6%)
Hematuria	12 (1.1%)	13 (1.7%)	17 (1.7%)	3 (0.4%)	34 (1.4%)
Proteinuria	3 (0.5%)	4 (0.5%)	2 (0.3%)	0	6 (0.3%)
Bladder, urethral symptoms	1 (0.2%)	3 (0.5%)	4 (0.6%)	4 (1.1%)	19 (1.0%)
Dysuria	0	3 (0.5%)	0	0	10 (0.6%)
Urinary tract lithiasis	5 (0.3%)	3 (0.3%)	9 (0.8%)	0	14 (0.5%)
Reproductive system, breast disorders	12 (10, 1.5%)	23 (18, 2.8%)	29 (18, 2.8%)	24 (16, 5.8%)	82 (57, 3.2%)
Metrorrhagia	0	3 (0.5%)	4 (0.6%)	0	9 (0.5%)
Respiratory, thoracic, mediastinal disorders	58 (39, 6.0%)	63 (42, 6.6%)	70 (50, 7.9%)	42 (31, 11.2%)	218 (149, 8.4%)
Upper respiratory tract sx,sy	7 (1.1%)	15 (2.0%)	10 (1.3%)	9 (3.2%)	51 (2.4%)
Pharyngolaryngeal pain	5 (0.8%)	11 (1.4%)	6 (0.8%)	9 (3.2%)	35 (1.7%)
Coughing, associated symptoms	18 (2.6%)	13 (1.9%)	16 (2.2%)	9 (2.5%)	53 (2.6%)
Nasal congestion, inflammation	3 (0.5%)	8 (1.3%)	8 (0.9%)	3 (1.1%)	21 (1.1%)
Bronchospasm, obstruction	2 (0.2%)	3 (0.5%)	1 (0.2%)	1 (0.4%)	15 (0.6%)
Dyspnea	3 (0.5%)	7 (0.5%)	7 (1.1%)	1 (0.4%)	11 (0.5%)
Nasal disorders NEC	11 (1.1%)	3 (0.5%)	5 (0.8%)	7 (1.8%)	17 (0.8%)
Epistaxis	10 (1.1%)	1 (0.2%)	3 (0.5%)	7 (1.8%)	13 (0.6%)
Skin, subcutaneous tissue disorders	51 (36, 5.6%)	99 (67, 10.5%)	108 (72, 11.3%)	66 (48, 17.3%)	347 (237, 13.4%)
Rashes, eruptions, exanthems	10 (1.5%)	26 (3.4%)	34 (4.4%)	16 (4.7%)	87 (4.0%)
Rashes	10 (1.5%)	24 (3.1%)	26 (3.5%)	13 (4.0%)	73 (3.4%)
Dermatitis, eczema	9 (1.2%)	14 (2.0%)	14 (1.9%)	2 (0.7%)	37 (1.8%)
Dermatitis allergic	0	6 (0.9%)	6 (0.9%)	0	13 (0.7%)
Pruritus NEC	4 (0.5%)	6 (0.9%)	12 (1.4%)	11 (2.9%)	42 (2.0%)
Pruritus	4 (0.5%)	3 (0.5%)	8 (0.9%)	9 (2.2%)	32 (1.5%)
Dermal, epidermal condit. NEC	4 (0.6%)	5 (0.8%)	3 (0.5%)	9 (2.9%)	27 (1.4%)
Urticarias	2 (0.3%)	5 (0.6%)	10 (1.3%)	3 (0.7%)	20 (0.9%)
Alopecias	1 (0.2%)	0	6 (0.9%)	11 (3.2%)	21 (1.0%)
Surgical medical procedures NEC	7 (7, 1.1%)	7 (7, 1.1%)	10 (10, 1.6%)	8 (6, 2.2%)	30 (27, 1.5%)
Vascular disorders	24 (20, 3.1%)	72 (54, 8.4%)	93 (70, 11.0%)	16 (14, 5.0%)	200 (156, 8.8%)
Vascular hypertensive disorders NEC	8 (1.2%)	41 (5.2%)	50 (6.8%	8 (2.2%)	108 (5.1%)
Hypertension	8 (1.2%)	39 (4.8%)	49 (6.6%)	8 (2.2%)	105 (4.9%)
Phlebitis	0	5 (0.8%)	5 (0.8%)	0	10 (0.6%)
Peripheral vascular dis. NEC	3 (0.5%)	4 (0.6%)	4 (0.5%)	3 (1.1%)	14 (0.7%)
Vascular hypotensivee disorders	3 (0.5%)	4).6%)	6 (0.8%)	0	10 (0.5%)
Hemorrhages NEC	3 (0.3%)	4 (0.5%)	6 (0.9%)	2 (0.7%)	13 (0.7%)
Hematoma	3 (0.3%)	4 (0.5%)	6 (0.9%)	2 (0.7%)	13 (0.7%)
Peripheral embolism, thrombosis	0	3 (0.3%)	6 (0.8%)	1 (0.4%)	12 (0.6%)

Source Table 8.1:10, pages 89 to 296 of 13,991. Adverse events are displayed as #AEs (#Pts, % Pts.). A patient experiencing more than one AE in a category is counted only once in that category.

Table s27-d. Common AEs ≥ 3% in PBO-controlled Trials in RA

Summary AEs for All SOC/HLT incidence ≥ 3% in PBO-Controlled Studies in RA					
Primary SOC, HLT	PBO N=647	CZP 200 mg [a] q2w N = 640	CZP 400 mg q2w N = 635	CZP 400 mg q4w N = 278	All CZP Doses N = 1774
Total Exp. pt.-yrs.	225	396	410	106	957
Total # Pts. w/ Any AE	404 (63%)	433 (68%)	425 (67%)	216 (78%)	1258 (79%)
Blood, lymphatic Syst.	24 (3.7%)	53 (8%)	43 (7%)	6 (2%)	110 (6%)
Cardiac disorders	13 (2%)	19 (3%)	22 (3.5%)	9 (3.2%)	60 (3.4%)
Congenital, genetic dis.	2 (0.3%)	1 90.2%)	2 (0.3%)	0	5 (0.3%)
Ear, labyrinth dis.	5 (0.8%)	9 (1.4%)	9 (1.4%)	5 (1.8%)	26 (1.5%)
Endocrine dis.	1 (0.2%)	5 (0.8%)	4 (0.6%)	0	11 (0.6%)
Eye dis.	15 (2%)	20 (3%)	33 (5%)	7 (2.5%)	69 (4%)
Gastrointestinal dis.	88 (13.6%)	85 (13.3%)	81 (12.8%)	57 (20.5%)	276 (15.6%)
GI, abd. Pains	11 (1.7%)	20 (3%)	16 (2.5%)	8 (3%)	51 (3%)
Diarrhea (exclu.infect)	18 (2.8%)	10 (1.6%)	9 (1.4%)	16 (5.8%)	44 (2.5%)
General dis,site admin.	110 (17%)	97 (15%)	78 (12%)	47 (17%)	272 (15%)
Injection, infusion site.	42 (6.5%)	42 (6.6%)	37 (5.8%)	17 (6.1%)	113 (6.4%)
Asthenic conditions	27 (4.2%)	26 (4.1%)	19 (3%)	18 (6.5%)	76 (4.3%)
Febrile disorders	11 (1.7%)	21 (3.3%)	18 (2.8%)	5 (1.8%)	49 (2.8%)
Pain, discomfort NEC	11 (1.7%)	7 (1.1%)	4 (0.6%)	9 (3%)	28 (1.6%)
Hepatobiliary disorders	7 (1.1%)	16 (2.5%)	11 (1.7%)	2 (0.7%)	30 (1.7%)
Immune system dis.	4 (0.6%)	5 (0.8%)	6 (0.9%)	5 (1.8%)	20 (1.1%)
Infections, infestations	148 (22.9)	239 (37.3%)	239 (37.6%)	103 (37.1%)	667 (37.6%)
Upper respirat.tr. Infec.	61 (9.4%)	107 (16.7%)	101 (15.9%)	55 (19.8%)	313 (17.6%)
Urinary tr. infec.	29 (4.5%)	40 (6%)	46 (7%)	6 (2%)	103 (6%)
Lower respir. tr. Infec.	22 (3.4%)	37 (5.8%)	37 (5.8%)	14 (5%)	100 (5.6%)
Bacterial infec.	11 (1.7%)	26 (4.1%)	29 (4.6%)	1 (0.4%)	59 (3.3%)
Viral infec. NEC	8 (1.2%)	25 (3.9%)	19 (3%)	2 (0.7%)	47 (2.6%)

(a.) Following 3 loading doses of CZP 400 mg each at Week 0, 2 and 4.
CZP=certoluzimab pegol; exclu = excluding; mg=milligrams; NEC=not elsewhere classified; PBO= placebo; Dis.=disorder; sx/sy = signs and symptoms; SOC=system organ class; tiss.= tissues.
Revised from table 2.7.4:20, pages 372 to 374 of 973

Table s27-e. *(Continued)* Common AEs ≥ 3% in PBO-controlled Trials in RA

Summary AEs for incidence ≥ 3% in PBO-Controlled Studies in RA					
Primary SOC, HLT	PBO N=647	CZP 200 mg [a] q2w N = 640	CZP 400 mg q2w N = 635	CZP 400 mg q4w N = 278	All CZP Doses N = 1774
Total Exp. pt.-yrs.	225	396	410	106	957
Herpes viral infect.	8 (1.2%)	20 (3.1%)	26 (4%)	10 (3.6%)	63 (3.6%)
Inections NEC	6 (0.9%)	19 (3%)	13 (2%)	3 (1.1%)	38 (2.1%)
Injury, poisoning, procedural complic.	34 (5%)	53 (8%)	58 (9%)	19 (6.8%)	145 (8%)
Investigations	66 (10%)	97 (15%)	112 (18%)	34 (12%)	272 (15%)
Liver Functions	31 (5%)	4 (7%)	54 (9%)	12 (4%)	119 (7%)
Metabolism/Nutrition	7 (1.1%)	14 (2.2%)	15 (2.4%)	6 (2.2%)	45 (2.5%)
Musculoskeletal and Connective Tiss. Dis.	121 (1.7%)	104 (16%)	97 (15%)	51 (18%)	326 (18.4%)
Musculoskeletal and CTD sx/sy MEC	27 (4%)	38 (6%)	41 (7%)	21 (8%)	119 (7%)
Neoplasms	6 (0.9%)	12 (1.9%)	9 (1.4%)	2 (0.7%)	28 (1.6%)
Nervous System Dis.	76 (12%)	56 (9%)	61 (9.6%)	61 (21.9%)	218 (12%)
Headaches	40 (6.2%)	33 (5%	26 (4%)	36 (12.9%)	123 (7%)
Paraesthesias and dysaethesias					
Neurological sx/sy NEC	12 (1.9%)	5 (0.8%)	9 (1.4%)	10 (3.6%)	32 (1.8%)
Pregnancy, puerpium perinatanl conditions	0	0	1 (0.2%)	0	1 (0.1%)
Psychiatric Disorders	27 (4.2%)	20 (3.1%)	18 (2.8%)	12 (4.3%)	63 (3.6%)
Renal, Urinary Disorders	16 (2.5%)	30 (4.7%)	29 (4.6%)	10 (3.6%)	82 (4.6%)
Reproductive System	10 (1.5%)	18 (2.8%)	18 (2.8%)	16 (5.8%)	57 (3.2%)
Respiratory, Thoracic, Mediastinal Disorders	39 (6%)	42 (7%)	50 (8%)	31 (11.2%)	149 (8.4%)
Upper Respirat. sx/sy	7 (1.1%)	13 (2%)	8 (1.3%)	9 (3.2%)	42 (2.4%)
Skin, Subcutaneous Tiss.	36 (5.6%)	67 (10.5%)	72 (11%)	48 (17%)	237 (13%)
Rashes, eruptions	10 (1.5%)	22 (3.4%)	28 (4.4%)	13 (4.7%)	71 (4%)
Alopecias	1 (0.2%)	0	6 (0.9%)	9 (3.2%)	17 (1%)
Surgical, Med. Procedures	7 (1.1%)	7 (1.1%)	10 (1.6%)	6 (2.2%)	27 (1.5%)
Vascular Disorders	20 (3%)	54 (8%)	70 (11%)	14 (5%)	156 (9%)
Vascular HTN Dis. NEC	8 (1.2%)	33 (5.2%)	43 (6.8%)	6 (2.2%)	90 (5.1%)

(a.) Following 3 loading doses of CZP 400 mg each at Week 0, 2 and 4.
CZP=certoluzimab pegol; exclu = excluding; mg=milligrams; NEC=not elsewhere classified; PBO= placebo; Dis.=disorder; sx/sy = signs and symptoms; SOC=system organ class; tiss.= tissues.
Revised from table 2.7.4:20, pages 372 to 374 of 973

Skin and Integument Adverse Events

In the PBO controlled studies, more TEAEs were observed in the category of skin and subcutaneous tissue disorders with CZP than with PBO (13%, 27.65 per 100 pt-yrs versus 6%, 5.28 per 100 pt-yrs, respectively).). The higher rate is accounted for by an increased rate of rash (3.4% versus 1.5%), allergic dermatitis (0.7% versus 0%), pruritus (1.5% versus 0.5%) urticaria (0.9% versus 0.3%) and alopecia (1% versus 0.2%). See **Table s27-c.**

Hypersensitivity Reactions and Delayed Hypersensitivity Reactions

Hypersensitivity reactions were defined as occurring within 2 hours of study drug administration. Delayed hypersensitivity reactions were defined as occurring between 2 hours and 14 days following study drug administration. In the PBO controlled studies, TEAES which could

represent hypersensitivity reaction were similar between the All CZP Doses group versus PBO control group (0.8% versus 0.5%). The HLT Pruritus NEC and the (PT) dizziness, flushing and dysphonia were included in this analysis. Study 011 and 014 employed sorbitol as the PBO agent. Sorbitol has been observed to be reactogenic. No Eosinophilia TEAEs or deaths were observed with hypersensitivity reactions.

Four patients withdrew due to early injection Hypersensitivity TEAEs:
- Pt. #007/013 (Study 027) experienced hypotension 17 minutes after CZP 200 mg injection and the event resolved in 15 minutes.
- Pt. #089/001 (Study 027) experienced allergic dermatitis approximately 2 hours after receiving CZP 400 mg. This reaction resolved 65 days later.
- Pt. #172/0013 (Study 051) experienced facial flushing 2 minutes after CZP injection. These symptoms resolved after 1 minute.
- Pt. #71/001 (Study 027) experienced a whole body rash, fever and breathing difficulties approximately 8 hours post the first injection of CZP 400 mg. The rash started at the injection site. Concurrent medications included MTX, salbutamol and nimesulide. His history included asthma. He was treated with paracetamol and the event resolved in 2 days. He was discharged from the study.

A total of 3 patients were observed with possible SAEs of Hypersensitivity reactions (e.g., angio-neurotic edema and or urticaria within 14 days of drug administration):
- Patient # 75225/1157 (Study 014) had angioneurotic edema (face, neck, arms, trunk and legs and hoarseness of her voice). History included arrhythmia, past episodes of erythema multiforme and fungal skin infections. Concomitant medications included MTX, alendronate, latanoprost and clotrimazole. A punch biopsy (upper arm) showed eosinophilic cellulitis. The study product was discontinued. MTX was continued. Her urticaria and angioedema resolved. Causality with the study product could not be excluded.
- Patient # 805/0003 (Study 050/051) experienced serum sickness. Prolonged fever with negative blood and urine cultures, negative Mantoux test, chest x-ray, abdominal CT, bone marrow and knee aspirations were reported. The serum sickness resolved with prednisone treatment. Causality to the study product could not be excluded.
- Patient #061/039 (Study 027/028) had urticaria (cervical, axillary, inguinal urticaria and whole-body pruritis). Concomitant medications included MTX, gliclazide and dlacrysin. She was successfully pretreated with dithiaden and methylprednisolone to prevent recurrence of urticaria with CZP sc injection. Causality to the study drug could not be excluded.

In the PBO controlled studies, the observed number of Delayed Hypersensitivity Reactions TEAEs (defined as from within 2 hours to 14 days post administration of study product) were higher in the All CZP Doses group versus PBO control group (14% versus 9%). The most common related TEAEs were headache (6%), rash (3%) and pyrexia (2.5%). In this safety database, concomitant MTX or anti-CZP antibody did not appear to affect these outcomes. As briefly described, a small number of SAEs in the CZP RA studies could be causally related to Hypersensitivity or Delayed Hypersensitivity reactions associated with the study product. The current CIMZIA® labeling includes ADVERSE REACTIONS, subsection *Other Adverse Reactions*, Skin and subcutaneous tissue disorders: (b) (4)

These outcomes support approval of the proposed lower CZP dose regimen, 200 mg q2w, as the maintenance treatment proceeded by a loading dose regimen of CZP 400 mg at Week 0, 2 and 4. In addition the labeling should also report the higher incidence of Skin and Subcutaneous Tissue Disorders TEAEs (noteworthy, a higher incidence in CZP 400 mg every 4 weeks (proposed as an alternative maintenance dose regimen) compared to CZP 200 mg q2w dose regimen.

7.4.2 Laboratory Findings

Laboratory data was pooled from the ISS (Studies 004, 011, 014, 027 and 050) comparing PBO-controlled studies and study periods. Laboratory data was pooled from OL studies (including the OL phase of 004 and OL Studies 015, 028 and 051) and from unpooled Study PHA 001 and 002. In patients who received PBO, Baseline values for OL treatment was the last value in the initial study (Study in which patient received PBO). For CZP treated patients in the patients in the initial study, the Baseline value for OL treatment was the same as the Baseline value for the initial study. Laboratory tests were reviewed for CZP RA Studies in hematology tests (e.g., RBC and WBC indices, platelets and clotting laboratory tests), chemistry tests (including liver function analyses, renal function tests, albumin and total protein, glucose, calcium and electrolytes). Analyses of auto-antibodies (ANA and anti-dsDNA) were also reviewed.

The mean change was from Baseline at Week 12 (e.g., mandatory discontinuation for lack of efficacy could take place). After Week 12, there were fewer patients remaining in the PBO control group. Because all patients who enrolled in PBO control studies did not continue in OL study options (OL phase of Study 004) or in OL Studies (015, 028 and 051), there is a smaller number of patients in the All RA Studies Population. The incidence of exposure was corrected per Amendment 5 submitted to the BLA on May 30, 2008 with revised incidence rates per 100 pt-yrs. OL safety data will be reported with data for periods of PBO control treatment. Laboratory test shifts to markedly abnormal values (CTCAE Grade 3 or 4) are also reviewed.

Hematology Laboratory Tests
No deleterious effects of CZP were observed in red cells, hemoglobin or hematocrit. See **Tables s28-a** and **s28-b.**

Table s28-a. RBC Indices: Summary of Mean Changes from Baseline (Week 12) and Last/ Withdrawal Visit Sponsor Table 2.7.4:57, page 530 of 973

Parameter (units)		Placebo N=635	CZP 200 mg[a] q2w N=640	CZP 400 mg q2w N=635	CZP400 mg q4w N=278	All CZP Doses N=1750
Red blood cells (10^{12}/L)	Week 12 BSL mean (SD)	4.349 (0.4388)	4.291 (0.4163)	4.283 (0.3959)	4.397 (0.4462)	4.310 (0.4140)
	Week 12 mean change (SD)	-0.027 (0.289)	-0.007 (0.283)	0.006 (0.2719)	0.054 (0.2399)	0.012 (0.269)
	Last/WD BSL mean (SD)	4.358 (0.4393)	4.295 (0.4192)	4.281 (0.3981)	4.382 (0.4457)	4.308 (0.4163)
	Last/WD mean change (SD)	-0.003 (0.303)	-0.011 (0.289)	-0.012 (0.2941)	0.045 (0.2664)	0.003 (0.283)
	Max. decrease from BSL mean (SD)	4.379 (0.4397)	4.314 (0.4178)	4.316 (0.3908)	4.406 (0.4342)	4.333 (0.4133)
	Mean max. decrease (SD)	-0.262 (0.2442)	-0.293 (0.2269)	-0.300 (0.2249)	-0.206 (0.1746)	-0.273 (0.2190)
Hemoglobin (g/L)	Week 12 BSL mean (SD)	129.13 (16.511)	126.71 (14.725)	127.54 (13.989)	131.96 (14.534)	127.65 (15.113)
	Week 12 mean change (SD)	-1.73 (8.55)	1.42 (8.66)	1.85 (8.756)	1.83 (7.486)	1.49 (8.43)
	Last/WD BSL mean (SD)	129.20 (16.157)	126.69 (14.682)	127.41 (13.935)	131.42 (14.391)	127.56 (14.991)
	Last/WD mean change (SD)	-1.77 (9.46)	1.16 (10.25)	1.22 (9.715)	1.74 (9.554)	1.18 (9.678)
	Max. decrease from BSL mean (SD)	129.83 (16.198)	127.81 (14.320)	128.73 (14.103)	133.47 (13.819)	128.70 (15.040)
	Mean max. decrease (SD)	-8.71 (7.023)	-8.31 (7.132)	-8.76 (6.635)	-6.85 (5.687)	-8.04 (6.634)
Hematocrit (fraction of 1)	Week 12 BSL mean (SD)	0.392 (0.0436)	0.387 (0.0407)	0.389 (0.0371)	0.396 (0.0407)	0.389 (0.0391)
	Week 12 mean change (SD)	-0.005 (0.026)	0.002 (0.026)	0.003 (0.0259)	0.005 (0.0238)	0.002 (0.026)
	Last/WD BSL mean (SD)	0.392 (0.0430)	0.387 (0.0404)	0.389 (0.0376)	0.395 (0.0403)	0.389 (0.0391)
	Last/WD mean change (SD)	-0.004 (0.030)	0.006 (0.031)	0.006 (0.0306)	0.004 (0.0294)	0.005 (0.030)
	Max. decrease from BSL mean (SD)	0.395 (0.0431)	0.390 (0.0397)	0.393 (0.0377)	0.400 (0.0384)	0.393 (0.0386)
	Mean max. decrease (SD)	-0.027 (0.0220)	-0.026 (0.0214)	-0.028 (0.0222)	-0.021 (0.0169)	-0.025 (0.0209)

[a] Following 3 loading doses of 400 mg each.

Table s28-b. Shift of Markedly Abnormal (Grade 3 or 4) RBC Indices- PBO control in CZP RA

Parameter	Worst Grade During Study	Placebo Baseline (n [%]) N	Low	Normal	High	All CZP Doses Baseline (n [%]) N	Low	Normal	High
Hemoglobin	Low Grade 4	635	1 (0.2%)	0	0	1750	4 (0.2%)	0	0
	Low Grade 3	635	5 (0.8%)	0	0	1750	5 (0.3%)	1 (0.1%)	0

Note: CZP = certolizumab pegol.
Sponsor Table 2.7.4:58, page 531 of 973.

White Blood Cell Indices

Mean white blood cell (WBC) values for all treatment groups were within normal limits at Baseline and remained normal at all time points. In the OL RA studies across all treatment groups, no clinically meaningful trends in mean actual values or changes from Baseline was observed. Shifts to markedly abnormally low WBCs were the same in the two treatment groups.

Neutrophils

In all treatment groups, the mean neutrophil values were within normal limits at Baseline and remained normal at all time points. A decrease from Baseline in mean neutrophil values was observed in the All CZP Doses group versus PBO control group (PBO controlled studies). One patient (Pt. # 209, Study 002) experienced a CTCAE low Grade 4 single neutrophil value (minimum value 1.36 x 109/L) throughout the CZP treatment. Concomitant medication included sulfasalazine at the time of the event. Treatment included reduction of the sulfasalazine dose. Causality for this event could not exclude the study product. Although a sustained decrease in mean neutrophil values was observed for all the CZP treatment groups, the decrease was not considered clinically meaningful. In the OL RA studies, mean neutrophil values were within normal limits at Baseline and remained as such at all time points in all treatment groups.
A higher percentage of patients in the All CZP Doses group (1.1%) had shifts to markedly abnormal low neutrophil values including 1% of patients with low Grade 3 abnormalities and

0.1% of patients with low Grade 4 abnormalities). In contrast, the PBO control group, 0.2% had shifts to markedly abnormal Grade 3 low neutrophil values and some had Grade 4. Only one Patient (Pt. #011/301, Study 004) with normal neutrophil values at Screening and Baseline experienced a low Grade 4 value. No cases of serious infection were associated with low neutrophil counts.

No excess of Eosinophilic Disorders TEAEs were observed considering the approximately 4-fold higher CZP exposure in the All CZP Doses group versus the PBO control group. One patient (Pt. # 062/001, Study 027) in CZP 400 mg q2w treatment group experienced extremely high eosinophil values. Concomitant medications included MTX, methylprednisolone, levothyroxine and omeprazole. Intermittant eosinophilia was first observed Week 6 (range 0.58 to 3.49 x 10^9/L) and increased through Week 44 (9.36 x 10^9/L). She experienced dysphagia and pyrexia. Eosinophil counts remained elevated at Week 48 and 52 (0.84 and 0.74 x 10^9/L, respectively). Elevated levels of eosinophils are sometimes associated with autoimmune disorders, e.g., rheumatoid arthritis, eosinophilic fascitis. Causality was unclear in the reported information. Eosinophilia may be associated with a variety of conditions and diseases, including asthma, allergy, connective tissue diseases, parasitic diseases and neoplasm.

Lymphocytes
No deleterous effects on lymphocytes were observed in these studies.

Platelets
In all treatment groups, mean platelets observed were in the high normal range at Baseline and at all time points. In the PBO controlled studies, a mean decrease in platelets in the All CZP Doses group versus placebo group was observed. This observed decrease is consistent with the finding of thrombocytosis as an acute-phase reactant and a return towards normal with decreased inflammation. See **Table s29-a.**

Prothrombin Time
In the PBO controlled studies, no significant change in mean prothrombin time (PT) was observed, All CZP Doses or PBO control group. A slightly higher percentage of patients in the All CZP Doses group (1.8%) had shifts to markedly abnormal Grade 3 high PT values compared with the PBO control (0.6%). This difference, however, does not consider the approximately 3-fold higher exposure in CZP treatment groups compared with PBO control.

Activated Partial Thromboplastin Time
In the PBO controlled studies, the activated partial thromboplastin time (aPTT) observed was higher in the All CZP Doses group versus a small decrease in the PBO control. The highest increase observed was in CZP 400 mg q2w treatment group. The mean highest increase was larger in the All CZP Doses group versus the PBO control group. See **Table s29-a.**

In the OL RA studies (all treatment groups) mean aPTT results were within normal limits at Baseline. In CZP 200 mg q2w treatment to CZP 400 mg q2w treatment; CZP 400 mg q2w treatment throughout; and PBO control treatment to CZP 400 mg q2w treatment, mean aPTT values were elevated above the ULN from Week 8 through Week 40.

This increase in aPTT is most likely an artifact of the assay. CZP appears to interfere with the human clinical aPTT assay. *In vitro* study results indicate interference and suggest that interference may be due to CZP, the Fab fragment or CZP (i.e., CZP minus the PEG moiety) or the PEG moiety itself. In pooled Study 001, no clinically meaningful changes in aPTT results were observed.

Shifts to markedly abnormal Grade 3 high aPTT values observed were (11.4%) in the All CZP Doses group versus (6.4%) in the PBO control group. See **Table s29-b.** This difference, however, does not consider the approximately 3-fold higher exposure in CZP treatment groups compared with PBO control.

International Normalized Ratio

In the PBO-controlled studies, no clinically meaningful trends in mean International Normalized Ratio (INR) or changes from Baseline were observed in All CZP Doses group or PBO control. See **Table s29-a**. No clinically meaningful difference was observed among the three CZP dose groups. In the OL RA studies (all treatment groups) mean INR values were within normal limits at Baseline and at all time points. A slightly higher percentage of patients (2.4%) in the All CZP Doses group versus (0.8%) in the PBO control observed shifts to markedly abnormal Grade 3 high INR values. In consideration of the longer exposure, this shift was not considered clinically meaningful. See **Table s29-b.**

Table s29-a. Parameters associated with Clotting: Mean changes from Baseline, Week 12 and Last/Withdrawal Visit in PBO-Controlled Studies Sponsor Table 2.7.4:61, page of 973.

Parameter (units)		Placebo N=635	CZP 200 mg[(a)] q2w N=640	CZP 400 mg q2w N=635	CZP400 mg q4w N=278	All CZP Doses N=1750
Platelets (10^9/L)	Week 12 BSL mean (SD)	327.0 (99.50)	337.5 (105.55)	333.0 (97.07)	316.2 (94.90)	330.7 (99.19)
	Week 12 mean change (SD)	1.4 (64.08)	-31.5 (68.03)	-33.2 (64.82)	-27.5 (53.63)	-28.8 (64.84)
	Last/WD BSL mean (SD)	327.1 (97.49)	337.5 (102.83)	333.5 (96.57)	322.2 (104.18)	331.8 (100.39)
	Last/WD mean change (SD)	8.6 (69.54)	-29.3 (77.10)	-33.4 (70.27)	-26.2 (64.74)	-27.9 (71.75)
	Max. decrease from BSL mean (SD)	337.8 (100.37)	342.1 (102.24)	336.5 (96.57)	327.5 (104.48)	335.6 (100.21)
	Mean max. decrease (SD)	-55.0 (52.11)	-85.8 (63.00)	-88.3 (62.02)	-71.7 (55.06)	-82.0 (60.20)
	Max. increase from BSL mean (SD)	321.9 (95.95)	318.8 (92.05)	315.8 (89.20)	303.5 (101.78)	314.9 (92.75)
	Mean max. increase (SD)	64.8 (55.12)	60.9 (59.45)	53.2 (52.96)	45.7 (50.04)	55.3 (55.74)
Prothrombin time (seconds)	Week 12 BSL mean (SD)	11.98 (3.076)	12.58 (3.015)	13.03 (6.801)	11.49 (1.238)	12.41 (4.488)
	Week 12 mean change (SD)	-0.14 (2.883)	0.06 (3.090)	-0.41 (6.353)	0.05 (0.861)	-0.11 (4.203)
	Last/WD BSL mean (SD)	12.04 (2.794)	12.53 (2.933)	13.04 (6.641)	11.51 (1.193)	12.36 (4.304)
	Last/WD mean change (SD)	0.08 (2.644)	0.46 (3.995)	0.12 (5.476)	0.12 (1.256)	0.23 (3.990)
	Max. increase from BSL mean (SD)	11.67 (1.625)	12.16 (2.100)	11.98 (1.427)	11.40 (0.956)	11.86 (1.610)
	Mean max. increase (SD)	1.53 (1.930)	3.67 (6.075)	3.95 (6.941)	0.95 (1.877)	2.90 (5.642)
aPTT (seconds)	Week 12 BSL mean (SD)	28.23 (9.391)	28.58 (8.869)	29.04 (8.966)	26.02 (4.076)	27.95 (7.862)
	Week 12 mean change (SD)	0.52 (16.540)	8.34 (16.726)	9.79 (13.568)	-0.20 (4.205)	6.23 (13.590)
	Last/WD BSL mean (SD)	27.80 (8.893)	28.91 (9.039)	29.08 (8.925)	26.21 (4.005)	28.07 (7.791)
	Last/WD mean change (SD)	-0.55 (10.130)	8.82 (16.020)	12.94 (17.445)	0.31 (5.839)	7.34 (15.009)
	Max. increase from BSL mean (SD)	26.63 (7.952)	28.61 (8.286)	28.34 (7.714)	25.51 (3.784)	27.62 (7.179)
	Mean max. increase (SD)	10.51 (22.535)	30.32 (25.456)	30.85 (23.785)	5.35 (10.772)	23.43 (24.408)

Table s29-a. Continued.

Parameter (units)		Placebo N=635	CZP 200 mg[(a)] q2w N=640	CZP 400 mg q2w N=635	CZP400 mg q4w N=278	All CZP Doses N=1750
INR	Week 12 BSL mean (SD)	1.043 (0.3080)	1.046 (0.2357)	1.077 (0.5036)	–	1.061 (0.3928)
	Week 12 mean change (SD)	-0.007 (0.3012)	0.007 (0.2436)	-0.026 (0.4679)	–	-0.009 (0.3727)
	Last/WD BSL mean (SD)	1.044 (0.3031)	1.041 (0.2290)	1.078 (0.4920)	–	1.060 (0.3841)
	Last/WD mean change (SD)	0.032 (0.2900)	0.042 (0.3276)	0.019 (0.4105)	–	0.031 (0.3713)
	Max. decrease from BSL mean (SD)	1.067 (0.3193)	1.067 (0.2428)	1.116 (0.5309)	–	1.091 (0.4107)
	Mean max. decrease (SD)	-0.142 (0.2979)	-0.138 (0.2359)	-0.178 (0.5096)	–	-0.158 (0.3949)
	Max. increase from BSL mean (SD)	1.008 (0.1712)	1.014 (0.1703)	1.000 (0.1127)	–	1.007 (0.1445)
	Mean max. increase (SD)	0.223 (0.1527)	0.303 (0.5003)	0.323 (0.5663)	–	0.313 (0.5337)

(a) Following 3 loading doses of 400 mg each.

Table s29-b. Shift of Markedly Abnormal (Grade 3or 4) Hematology Values Associated with Clotting in PBO-Controlled Studies Sponsor Table 2.7.4:62, page 545 of 973

Parameter	Worst Grade During Study	Placebo Baseline (n [%]) N	Low	Normal	High	All CZP Doses Baseline (n [%]) N	Low	Normal	High
Platelets	Low Grade 4	635	0	0	0	1750	0	0	1 (0.1%)
	Low Grade 3	635	0	0	1 (0.2%)	1750	0	0	0
Prothrombin time	High Grade 3	353	0	1 (0.3%)	1 (0.3%)	729	0	10 (1.4%)	3 (0.4%)
aPTT	High Grade 3	353	5 (1.4%)	15 (4.2%)	3 (0.8%)	729	13 (1.8%)	55 (7.5%)	15 (2.1%)
INR	High Grade 3	125	0	0	1 (0.8%)	494	0	9 (1.8%)	3 (0.6%)

Notes: aPTT = activated partial thromboplastin time; CZP = certolizumab pegol; INR = international normalized ratio.

Overall in the PBO-controlled studies, elevated baseline platelet counts, which are known to be associated with chronic inflammation of RA, were observed to decrease with CZP treatment. This CZP treatment effect is most likely due to decreased inflammation.

The mean change in aPTT was higher in CZP treatment versus in PBO control. When corrected for approximately 3-fold higher exposure in CZP treatment groups versus PBO control, CZP treatment effect is less likely for markedly abnormal values with CZP treatment. The literature suggests an artifactual interference on the human clinical aPTT assay by PEG. Bleeding AEs observed did not increase with increased aPTT.

In summary, clinically meaningful treatment effect on clotting parameters appears to be unlikely. The current labeling reflects WARNINGS AND PRECAUTIONS section, Hematological Reactions subsection, bruising or bleeding while on CIMZIA; and ADVERSE REACTIONS section, *General disorders and administration* subsection reflects injection site hematoma and injection site bruising.

Overall in the PBO-controlled studies, CZP did not show an adverse treatment effect on RBCs or WBC indices. An increase in hemoglobin and hematocrit consistent with a CZP treatment effect of improvement in anemia of chronic disease was observed. In addition, CZP treatment effect of decrease in platelets consistent with decrease in acute phase reactants secondary to decreased inflammation was observed.

Chemistry - Liver Function Tests

Aspartate Aminotransferase and Alanine Aminotransferase

In all treatment groups, mean aspartate aminotransferase (AST) values were normal at all time points. A small increase in mean AST from Baseline was observed in the All CZP Doses group versus the PBO control group in the PBO-controlled studies. This small increase was not considered clinically meaningful. In the PBO-controlled studies, shifts to markedly elevated liver function analyses (Grade 3 or 4) were observed in < 1% in both CZP treated and PBO control treated patients. A small number of patients were observed with shifts from normal Baseline values to Grade 3: AST (2 patients, 0.3%), in ALT (4 patients, 0.6%) in GGT (14 patients, 2.2%). There were no shifts observed from normal Baseline to Grade 4 in any CZP treated patients. See **Table s30.**

Alanine Aminotransferase

In all treatment groups, mean ALT values were within normal limits at Baseline and at all time points. In the PBO-controlled studies, no clinically meaningful change from Baseline in mean ALT value was observed in the All CZP Doses group versus the PBO group. In OL RA studies, no clinically meaningful trends were observed overtime. The percentage of shifts to markedly abnormal (Grade 3 or 4) ALT was similar in CZP treatment groups. See **Table s30.**

Gamma-Glutamyl Transferase

No clinically meaningful change from Baseline in mean GGT value was observed in the All CZP Doses group versus PBO control, in the PBO-controlled studies. In the OL RA studies, no trend in mean GGT over time was observed. See **Table s30.**

Alkaline Phosphatase

No meaningful shifts were observed across CZP treatment groups compared to the PBO control group. No patients in the All CZP Doses group experienced a shift to Grade 4 high alkaline phosphatase. See **Table s30.**

Total bilirubin

A small mean increase from Baseline in total bilirubin was observed in the All CZP Doses group versus PBO control group in the PBO-controlled trials, however, this increase was not clinically meaningful. In the OL RA studies, in all treatment groups, mean total bilirubin was normal at Baseline through the study end. See **Table s30**. One patient (Pt. #011/014, Study 028) experienced Grade 3 elevations of hepatic enzymes in combination with a bilirubin value ≥ 3 x ULN. There were no shifts to markedly abnormal (Grade 3 or 4) high total bilirubin in the All CZP Doses group or in the PBO control across the PBO-controlled studies.

Table s30. Shifts of Markedly Abnormal (Grade 3 or 4) Liver Function Analyses – PBO control

Parameter	Worst Grade During Study	Placebo Baseline (n [%]) N	Low	Normal	High	All CZP Doses Baseline (n [%]) N	Low	Normal	High
AST	High Grade 3	635	0	1 (0.2%)	2 (0.3%)	1750	0	9 (0.5%)	5 (0.3%)
	High Grade 4	635	0	1 (0.2%)	0	1750	0	0	0
ALT	High Grade 3	635	0	3 (0.5%)	4 (0.6%)	1750	0	11 (0.6%)	14 (0.8%)
	High Grade 4	635	0	1 (0.2%)	0	1750	0	0	0
GGT	High Grade 3	635	0	2 (0.3%)	14 (2.2%)	1750	0	6 (0.3%)	20 (1.1%)
	High Grade 4	635	0	0	0	1750	0	0	1 (0.1%)
Alkaline phosphatase	High Grade 3	635	0	0	0	1750	0	0	2 (0.1%)
	High Grade 4	635	0	0	0	1750	0	0	0

Note: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CZP = certolizumab pegol; GGT = gamma-glutamyl transferase.

Parameter (units)		Placebo N=635	CZP 200 mg[(a)] q2w N=640	CZP 400 mg q2w N=635	CZP400 mg q4w N=278	All CZP Doses N=1750
	Week 12 mean change (SD)	1.4 (26.74)	-5.9 (22.05)	-6.9 (18.18)	-5.5 (15.37)	-5.9 (19.66)
	Last/WD BSL mean (SD)	89.5 (33.41)	88.5 (35.50)	88.0 (30.46)	88.1 (33.89)	89.1 (32.93)
	Last/WD mean change (SD)	0.6 (25.94)	-5.2 (26.01)	-6.2 (26.56)	4.5 (17.96)	-5.3 (24.58)
	Max. increase from BSL mean (SD)	86.3 (28.24)	85.7 (34.88)	85.2 (30.21)	85.4 (35.26)	86.3 (32.62)
	Mean max. increase (SD)	16.4 (24.52)	18.0 (27.70)	17.3 (31.33)	15.1 (19.00)	17.1 (26.92)
Total bilirubin (µmol/L)	Week 12 BSL mean (SD)	7.253 (3.343)	6.975 (3.660)	7.093 (3.356)	7.409 (3.428)	7.080 (3.442)
	Week 12 mean change (SD)	0.115 (3.009)	0.750 (3.149)	0.747 (3.009)	0.640 (3.275)	0.701 (3.065)
	Last/WD BSL mean (SD)	7.216 (3.345)	6.999 (3.686)	7.070 (3.262)	7.177 (3.333)	7.043 (3.399)
	Last/WD mean change (SD)	-0.019 (2.943)	1.018 (3.429)	1.051 (3.393)	0.514 (3.172)	0.885 (3.304)
	Max. increase from BSL mean (SD)	6.910 (3.132)	6.794 (3.473)	7.055 (3.332)	6.969 (3.147)	6.910 (3.301)
	Mean max. increase (SD)	2.933 (2.869)	4.675 (4.359)	4.348 (3.492)	3.270 (3.074)	4.172 (3.731)

[(a)] Following 3 loading doses of 400 mg each.

Sponsor Table 2.7.4:62-63, pages 552-553 of 973.

Other Chemistry Laboratories

Treatment with CZP did not show a clinically meaningful adverse treatment effect for liver function analyses, renal function tests, albumin and total protein, glucose, total calcium or electrolytes (potassium and sodium). An increase in albumin over time in CZP treatment groups versus PBO-control was observed and this was consistent with an improvement in chronic disease. Although no clinically meaningful outcomes were reported with the total calcium as measured, it is important to note that total calcium was not corrected for albumin and ionized calcium was not reported in this safety database.

Autoantibody Assays

In the PBO-controlled studies, CZP did not appear to have an effect on the formation of auto-antibodies (ANA and anti-dsDNA). Autoantibody data for the PBO-controlled studies included Study 004, 011, 014, 027 and 050). In the PBO-controlled safety data, the percent at Baseline was reported as the number of patients who experienced the event (e.g., a change from the Baseline value) and the denominator was reported as the total number of patients. The OL safety data included Study 004, 015, 028 and 051). Safety data from unpooled Study 001 and 002 were included where relevant. Baseline values were defined as the last value before receiving the study product, regardless of study phase. For the Last or Withdrawal Visit, the denominator for percentages was defined as all patients.

Antinuclear Antibodies

The data on ANA submitted are difficult to interpret because the baseline positive titers are much higher than expected. Approximately 60-76% of patients were positive at baseline in the various Phase 3 studies, much higher than the expected rates for patients with RA. (See **Table s31**) These findings suggest a problem with the assay. Studies of other TNF blockers have shown increases in conversion to positive ANA.

Table s31. Maximum changes from Baseline in ANA in PBO-Control CZP RA Studies

Maximum Changes from Baseline in ANA - PBO-controlled CZP RA Studies Corrected data from Amendment 5, submitted May 30, 2008						
N	Baseline Category	Baseline n (%)	< 2 x ULN	≥2 to < 4 x ULN	≥ 4 x ULN	Missing
Placebo						
635	< 1:160	357 (56%)	278 (44%)	41 (6.5%)	2 (0.3%)	36 (6%)
CZP 200 mg q2w						
640	< 1:160	243 (38%)	177 (28%)	52 (8%)	7 (1.1%)	7 (1.1%)
CZP 400 mg q2w						
635	< 1:160	248 (39%)	172 (27%)	59 (9%)	6 (0.9%)	11 (1.7%)
CZP 400 mg q4w						
278	< 1:160	218 (78.4%)	189 (68%)	13 (5%)	1 (0.4%)	15 (5%)
All CZP Doses						
1750	< 1:160	868 (50%)	683 (39%)	130 (7%)	15 (0.9%)	40 (2.3%)

Sponsor Table 8:17, Amendment 5 submitted May 30, 2008

Anti-Double-Stranded DNA Antibodies

A total of 4 patients were observed to have systemic lupus erythematosus (SLE) at screening. Predefined eligibility criteria should have excluded these 4 patients. All 4 patients received CZP treatment; 1 patient (CZP 400 mg q2w); 3 patients (CZP 400 mg q4w) and 2 patients (PBO prior to CZP). As shown in **Table s32**, few patients with anti-dsDNA less than 2 x ULN at baseline developed elevated anti-dsDNA during the study: 0.8% of PBO-treated patients versus 1.7% of CZP treated patients. Interpretation of these data is complicated by the fact that approximately 25% of all patients were positive (>2 x ULN) at baseline.

In summary, in the PBO-controlled RA studies, small numbers of CZP-treated patients developed increases in ANA or anti-dsDNA conversion. The current labeling reflects this conclusion. Conclusions are limited because of the surprisingly high proportion of patients who were positive at baseline.

Table s32. Maximum changes from Baseline in Anti-dsDNA – PBO-Controlled Studies

Maximum Changes from Baseline in Anti-dsDNA - PBO-controlled CZP RA Studies Corrected data from Amendment 5, submitted May 30, 2008						
N	Baseline Category	Baseline n (%)	< 2 x ULN	≥2 to < 4 x ULN	≥ 4 x ULN	Missing
Placebo						
635	<2 x ULN	479 (75.4%)	369 (58.1%)	3 (0.5%)	2 (0.3%)	105 (16.5%)
CZP 200 mg q2w						
640	< 2 x ULN	507 (79.2%)	449 (70.2%)	4 (0.6%)	8 (1.3%)	46 (7.2%)
CZP 400 mg q2w						
635	< 2 x ULN	490 (77.2%)	432 (68%)	2 (0.3%)	10 (1.6%)	46 (7.2%)
CZP 400 mg q4w						
278	< 2 x ULN	191 (68.7%)	123 (44.2%)	4 (1.4%)	0	64 (23.0%)
All CZP Doses						
1750	< 2 x ULN	1369 (78.2%)	1175 (67.1%)	12 (0.7%)	18 (1.0%)	164 (9.4%)

Note: CZP= certoluzimab; ULN=upper limit of normal (range).

Lupus-Like Illness and Auto-Antibodies
In the PBO-controlled studies, a similar percentage of patients experienced TEAEs of ANA positive, ANA increased and anti-dsDNA positive in the All CZP Doses group (0.5%, 0.2% and 0%, respectively) versus in PBO-control (0.2%, 0.5% and 0%, respectively). In the OL All RA Studies (in the All CZP Doses group), ANA positive, ANA increased and anti-dsDNA positive TEAEs occurred at lower rates per 100 pt-yrs than the corresponding incidence rates in the PBO-controlled studies. Overall, there did not appear to be increased risk with longer CZP exposure. The lupus-like events observed in this safety database are shown in **Table s33.**

Table s33. Summary of Lupus-like AEs in the Safety Population

Lupus-like Events during CZP Studies (Safety Population)				
HLT, Pt #, Study #	Preferred Term	Severity	Time (days) from 1st to onset	Outcome
Lupus Erythematosus				
26/605 (Study 004)	SLE	Moderate	16	Resolved
007/007 (Study 028)	Lupus like syndrome	Moderate	224	Resolved
008/004 (Study 028)	Lupus like syndrome	Moderate	322	Ongoing
Cutaneous lupus erythematosus				
63947/1082 (Study 015)	Cutaneous lupus erythematosus	Mild	680	Ongoing
Connective tissue disoders				
802/0003 (Study 051)	SLE	Mild	27	Resolved
53682/1212 (Study 015)	SLE	Moderate	807	Resolved

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7.4.3 Vital Signs

Vital Signs and Blood Pressure
In the PBO-controlled studies, systolic and diastolic blood pressure (BP) safety data (Study 004, 011, 014, 027 and 050) were pooled. Due to pre-specified differences in the timing of assessments, respiratory rate and pulse rate among these studies, data was not pooled for these measurements. See **Table s34** summarizes the mean change from Baseline at Week 12 and Last/withdrawal Visit in assessments, including vital signs assessments. Vital signs safety data was not summarized in ongoing OL studies (e.g., Studies 015, 028 and 050).

In the PBO-controlled RA studies, no clinically meaningful changes between pre-dose and post-dose BP values or trends over time were observed. More Hypertension TEAEs were observed in CZP treatment groups versus in the PBO-control group. Irrespective of whether a patient had a history of hypertension at Baseline, CZP treatment was not associated with a higher risk of developing hypertension.

Pulse Rate, Respiratory Rate and Temperature
In the RA studies (Studies PHA 001, 002, 004, 027 and 050) no clinically meaningful treatment effects on pulse rate, respiratory rate and body temperature were observed for CZP treated patients versus PBO-control patients.

Table s34. Blood Pressure: Mean Changes from Baseline at Week 12 and Last/Withdrawal Visit – PBO-controlled Studies

Parameter (mmHg) Time Relative to Dosing		Placebo N=635	CZP 200 mg[a] q2w N=640	CZP 400 mg q2w N=635	CZP400 mg q4w N=278	All CZP Doses N=1750
Systolic Blood Pressure						
Pre-Dose	Week 12 BSL mean (SD)	128.9 (15.77)	126.6 (15.66)	126.7 (16.13)	131.0 (18.81)	127.3 (16.41)
	Week 12 mean change (SD)	-1.5 (14.77)	-1.9 (14.01)	-1.5 (14.39)	-2.1 (16.79)	-1.8 (14.59)
After Dosing	Week 12 BSL mean (SD)	128.9 (15.79)	126.6 (15.66)	126.7 (16.15)	131.0 (18.74)	127.3 (16.40)
	Week 12 mean change (SD)	-2.0 (14.04)	-1.5 (14.07)	-2.2 (14.16)	-2.6 (16.03)	-2.0 (14.40)
Not Applicable	Last/WD BSL mean (SD)	129.2 (16.07)	127.0 (15.95)	126.7 (16.16)	129.6 (18.16)	128.0 (16.75)
	Last/WD mean change (SD)	-1.7 (15.03)	-2.4 (14.09)	-1.4 (14.43)	-2.2 (15.48)	-2.0 (14.46)
Diastolic Blood Pressure						
Pre-Dose	Week 12 BSL mean (SD)	78.5 (9.87)	78.4 (9.22)	78.0 (9.87)	78.7 (9.95)	78.3 (9.61)
	Week 12 mean change (SD)	-0.2 (9.20)	-1.2 (8.79)	-0.6 (9.69)	-0.1 (9.55)	-0.8 (9.30)
After Dosing	Week 12 BSL mean (SD)	78.5 (9.88)	78.4 (9.22)	78.1 (9.89)	78.7 (10.00)	78.3 (9.62)
	Week 12 mean change (SD)	-0.7 (9.29)	-1.0 (9.38)	-0.4 (9.25)	-1.1 (9.69)	-0.8 (9.37)
Not Applicable	Last/WD BSL mean (SD)	78.3 (9.89)	78.5 (9.32)	78.1 (9.85)	78.1 (10.08)	78.4 (9.71)
	Last/WD mean change (SD)	-0.4 (9.41)	-1.4 (9.13)	-0.8 (9.84)	-0.4 (9.46)	-0.9 (9.58)

[a] Following 3 loading doses of 400 mg each.

7.4.4 Electrocardiograms (ECGs)

Due to pre-specified differences in the timing of schedules and the frequency of collection of ECG data across the RA studies, these data were not pooled in the ISS. ECGs were classified as normal or abnormal by the Investigator. Serial ECG data for CZP 200 mg q2w was only collected in Study 004. The remaining studies with serial ECG data were conducted with CZP 400 mg q4w treatment. Abnormal ECG findings were classified as clinically significant or not clinically significant and the latter recorded in the Medical History at screening or as an AE if treatment emergent. Overall, serial ECGs, as assessed by the Investigators, did not show any pattern of abnormalities in the subset of RA studies in which they were collected. Electrocardiogram interval data, including QTc, were not collected for the RA studies. QT_c data was collected in Study PHA-024 (Health Volunteers, HV).

- Study PHA-024: one patient in the pooled HV population (Pt. #102) experienced sinus bradycardia with nodal escape. Since this event is an abnormal variant commonly observed in healthy young adults, causality to the study product was considered unlikely.

Also observed in Study PHA 024 were two ECG abnormalities noted on Baseline to Day 1 testing which were significantly different (p-value ≤ 0.05) between the treatment groups: 1) Maximum QRS interval was statistically significantly different between the treatment groups for both Caucasian and Japanese patients and 2) the maximum uncorrected QT interval was statistically significantly different between the treatment groups for Japanese patients. QT intervals [corrected for heart rate (QTc)], however, did not appear to be affected by this abbrency and no extreme abnormal values [defined as >460 milliseconds (msec)] for any of the QT parameters (QT interval, QTc [Bazett], QTc [Fridericia]) were observed in any treatment group.

This suggests that these findings in the maximum QRS and uncorrected QT parameters are not clinically meaningful.

Overall, from the subset of patients in which ECGs were collected, there does not appear to be a cardiovascular pattern or signal of abnormal cardiovascular events and ECG abnormalities in patients treated with CZP. Note: Electrocardiogram interval data, including QTc was not collected for the RA studies.

7.4.5 Special Safety Studies

7.4.6 Immunogenicity

Anti-Certoluzimab Pegol Antibody Status across PBO-Controlled CZP RA Studies
A total of 105 out of 1,508 patients (7%) in the CZP RA trials (Studies 011, 014, 027 an compared to 2% with CZP monotherapy became anti-CZP antibody positive. A total of 6% of patients receiving background MTX became anti-CZP antibody positive. See **Table s35-a.** In the Phase 3 studies at Week 26 (CZP 200 mg and CZP 400 mg q2w + MTX treatment groups), anti-CZP antibody-positive patients (by percentages) were similar with the lyophilized and liquid formulations. See **Table s35-b.**

Table s35-a. Anti-CZP Antibody Positive Patients in CZP RA Studies

Anti-CZP Antibody Positive Patients - Study 011, 014, 027 and 050 in RA					
	CZP 200 mg [a.] sc q2w + MTX N = 640	CZP 400 mg sc q2w + MTX N = 633	CZP 400 mg sc q4w + MTX N = 124	CZP 400 mg sc N = 111	All CZP Doses N = 1508
Antibody Positive	63 (10%)	12 (2%)	5 (4%)	25 (22.5%)	105 (7%)

Notes: CZP = certolizumab pegol; MTX = methotrexate; N/A = not applicable; q2w = every 2 weeks; q4w = every 4 weeks. Sponsor Table 2.7.4:24, page 387 of 973

Table s35-b. Anti-CZP Antibody Positive Patients at Week 26 by CZP Formulation

Anti-CZP Antibody Positive Patients by Week 26 by Formulation					
	CZP 200 mg [a.] sc q2w + MTX N = 640	CZP 400 mg sc q2w + MTX N = 633	CZP 400 mg sc q4w + MTX N = 124	CZP 400 mg sc N = 111	All CZP Doses N = 1508
Antibody Positive	63 (10%)	12 (2%)	5 (4%)	25 (23%)	105 (7%)

Notes: CZP = certolizumab pegol; MTX = methotrexate; N/A = not applicable; q2w = every 2 weeks; q4w = every 4 weeks. Sponsor Table 2.7.4:24, page 387 of 973

Adverse Events by Anti-CZP Antibody Status
All patients in the PBO-controlled studies pooled database were reviewed. Dose-finding Studies 002 and 004 (which employed the first liquid formulation which was reformulated) were also included. Patients who developed anti-CZP antibodies only at the Week 12 follow-up visit after withdrawal were also included.

Antibody can bind to antigen *in vivo* and form immune complexes which are normally cleared through the reticuloendothelial system. If the antibody binds in the active site, it may neutralize

the binding of the therapeutic antibody to its antigen. Where antibodies bind elsewhere on the molecule, they will circulate as immune complexes and may have a shorter half-life than the study product alone. In this case, they will be considered clearing antibodies. Both neutralizing and clearing antibodies may reduce efficacy and affect safety.

The data from CZP treatment groups were analyzed as follows: for patients who eventually became antibody-positive, TEAEs starting before the first antibody-positive result and TEAEs starting on or after the first antibody-positive result are summarized separately, as were TEAEs for patients who were always antibody-negative. See **Table s37.** The proportion of patients with AEs was not increased in patients who were antibody-positive than in patients who were antibody-negative. There was also no tendency for antibody-positive patients to have more severe AEs or to withdraw more frequently due to AEs. The rate of TEAEs was 69% in patients who were anti-CZP antibody negative. The rate of serious TEAEs (8%) were similar in the two assays compared to the rate of severe TEAEs (10% versus 7%), in patients prior to the first antibody detection versus in patients with antibody. See **Table s37.**

TEAEs leading to withdrawal (7% versus 2%) were lower based on re-testing and the positive antibody status. See **Table s37.** There was not a category of SOC that was more frequent in antibody-positive patients than in antibody-negative patients.

Table s37. Summary of AEs in All CZP Doses Group by Anti-CZP Antibody Status Prior to the AE in PBO-Controlled CZP RA Studies

Summary of AEs in the All CZP Doses Group by Anti-CZP Antibody Status Prior to the AE in PBO-Controlled CZP RA Studies			
	Events Starting Prior to 1st Ab+ Result	Events Starting On or After 1st Ab+ Result	Events for Pts. who Remained Ab -
Number of Pts. with any AE	159 (72%)	107 (49%)	1072 (69%)
Intensity [a.]			
Mild	123 (56%)	69 (31%)	878 (57%)
Moderate	99 (45%)	54 (24%)	605 (39%)
Severe	22 (10%)	16 (7%)	138 (9%)
Serious AEs	17 (7.7%)	17 (7.7%)	157 (10%)
AEs Leading to Withdrawal [b.]	9 (7%)	2 (2%)	65 (5%)

Revised sponsor Table 2.7.4:26, page 388 of 973. Notes: Ab+ = Antibody-positive; Ab- = Antibody-negative; CZP = certolizumab pegol. Events are displayed as number of subjects (percent of subjects). A patient experiencing more than 1 event in a category was counted only once in that category. Positive anti-CZP Ab level was defined as >2.4 units/milliliter; negative was defined as ≤2.4 units/milliliter.
(a) Adverse events with changing intensity over time were included only for the maximum intensity.
(b) Due to case report form design, events leading to withdrawal from Studies 002 and 004 could not be identified for inclusion. Percentages are calculated from the sub-population excluding these studies.

In patients who developed anti-CZP antibody, rates of TEAEs were higher in the first assay versus the second assay for SOC GI Disorders (15% versus 6%), General Disorders and Administration Site conditions (22% versus 9%), Infections 32% versus 16%), Musculoskeletal and Connective Tissue Disorders (16% versus 8%). See **Table s38.**

Table s38. AEs with a ≥ 1% Higher Incidence between AEs that Started Before or On After the First Anti-body Positive Result and AEs in Patients who Remained Antibody Negative (All CZP Doses Group) by Anti-CZP Antibody Status in PBO-Controlled Trials

AEs Having ≥ 1% Higher Incidence Between AEs that Started Before or On After the First Antibody Positive Result and AEs in Patients who Remained Antibody-Negative (All CZP Doses Group) by Anti-CZP Status - PBO-Controlled Studies			
	All CZP Doses		
Primary SOC High Level Term	Prior to First AB+ Result N = 221	On or After First Ab+ Result N = 221	Remained Ab- N = 1552
Gastrointestinal disorders	32 (15%)	13 (6%)	235 (15%)
GI and abdominal pains	8 (4%)	2 (0.9%)	41 (3%)
General disorders and admin. site conditions	49 (22%)	19 (9%)	213 (14%)
Febrile Disorders	12 (5%)	4 (2%)	34 (2%)
General signs and symptoms NEC	5 (2%)	1 (0.5%)	16 (1%)
Injection and infusion site reactions	22 (10%)	9 (4%)	87 (6%)
Infections and Infestations	70 (32%)	35 (16%)	575 (37%)
Injury, poisoing and procedural complic.	12 (5%)	5 (2%)	129 (8%)
Non-site specific procedural complic.	3 (1.4%)	0	6 (0.4%)
Investigations	25 (11%)	15 (7%)	234 (15%)
Tissue enzyme analyses NEC	5 (2%)	2 (0.9%)	9 (0.6%)
Musculoskeletal, connnective tissue dis.	43 (20%)	30 (14%)	263 (17%)
Rheumatoid arthropathies	20 (9%)	15 (7%)	64 (4%)
Nervous system disorders	26 (12%)	7 (3%)	185 (12%)
Headaches NEC	17 (8%)	6 (3%)	100 (6%)
Psychiatric disorders	8 (4%)	1 (0.5%)	54 (4%)
Disturbanc. in initiating, maintain. sleep	5 (3%)	1 (0.5%)	17 (1%)
Respiratory, throacic, mediastinal dis.	23 (10%)	10 (5%)	119 (8%)
Coughing, associated symptoms	9 (4%)	5 (2%)	32 (2%)
Upper respiratory tract sx. and sy.	11 (5%)	3 (1%)	31 (2%)
Skin, subcutaneous tissue disorders	35 (16%)	17 (8%)	190 (12%)
Urticarias	4 (2%)	2 (0.9%)	10 (0.6%)
Dermal, epiderman conditions NEC	5 (2%)	3 (1.4%)	18 (1.2%)
Erythemas	5 (2%)	1 (0.5%)	15 (1)

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Notes: Ab+ = antibody-positive; Ab- = antibody-negative; NEC = not elsewhere classified.

In summary, there was no evidence that anti-CZP antibodies were associated with a worse safety profile or with specific TEAEs. It was noteworthy that the incidence of TEAEs possibly associated with hypersensitivity events (e.g., injection site reactions, other immunological events) did not appear to be increased in the presence of anti-CZP antibody formation.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A higher incidence of TEAEs was observed in CZP treatment groups compared to the PBO-control group. No clinically meaningful dose effect for TEAEs was observed in these studies. The absolute incidence of TEAEs was higher in CZP 400 mg q4w group compared with the other CZP treatment groups. There does not appear to be a biologically based reason for why the lower monthly dose frequency of CZP 400 mg q4w versus CZP 400 mg q2w would have a less favorable profile. Therefore, the higher rate of TEAEs with the 400 mg q4w dose may have been a unique feature of that particular trial and not a reflection of a dose-dependent effect.

In the PBO-controlled studies, a higher percentage of patients receiving CZP experienced SAEs (11%, 19.95 per 100 pt-yrs) compared with patients receiving PBO-control (7%, 18.01 per 100 pt-yrs). No dose-related differences were noted in the overall incidence of SAEs across the 3 CZP dose regimens.

7.5.2 Time Dependency for Adverse Events

Up to the first 30 months of CZP exposure, the incidence of any AE, SAE, AEs leading to death and AEs leading to withdrawal showed no evidence of increase with time using 6-month intervals.

7.5.3 Drug-Demographic Interactions

Age, Sex and Duration of RA Disease
In the PBO-controlled studies, overall TEAEs and SAEs by SOC, HLT and PT were reviewed for the All Studies RA population by gender, age, race, baseline BMI and geographic region. The trial populations consisted of a majority of women (80%) who were 53 years of age with established RA (8 years duration) on background RA therapy who met the ACR criteria for RA. No trend toward increased TEAEs was observed of either gender and no clinically meaningful trend in SAEs was observed with gender. In the PBO-controlled studies, All CZP Doses treatment group, the overall incidence of TEAEs and SAEs was slightly higher in the ≥ 65 years age group versus the 18 to 64 years group. The incidence of most events was similar across all ages. Only a small number of patients ≥ 65 years were observed in each treatment group. Overall, it was difficult to reach a meaningful conclusion based on these data.

Body Mass Index
In the PBO-controlled studies, All CZP Doses group, a similar percentage of patients with a Baseline BMI of ≥30 kg/m^2 versus with a Baseline BMI of <25 or 25 to <30 had at least at least 1 TEAE (74% versus 69% and 0.3%, respectively). No clinically meaningful trend in TEAEs across Baseline BMI groups was observed for most SOCs.

7.5.4 Drug-Disease Interactions

Renal and Hepatic Impairment
Patients with clinically significant renal or hepatic impairment were excluded from the CZP RA trials based on pre-defined eligibility criteria.

Hypertension
Patients with a history of hypertension (at baseline) had increased hypertension TEAE compared to patients without a history of hypertension. In the PBO-controlled studies, 46 out of 1194 patients (4%) without hypertension (at Baseline) and 47 out of 556 patients (9%) with hypertension at Baseline, in the All CZP Doses group experienced hypertensive TEAEs. In the PBO-control group, a similar pattern was observed: 5 out of 433 patients (1%) without hypertension (at Baseline), and 4 out of 202 patients (2%) with hypertension at Baseline, experienced hypertensive TEAEs. Considering the 4-fold differences in exposure, CZP treatment

group versus PBO control group, no clinically meaningful trend toward increased hypertension TEAEs was observed with higher CZP dose (200 mg versus 400 mg) or dosing frequency (q2w versus q4w). Overall, the mean change from Baseline in systolic and diastolic BP was similar in CZP treatment groups and PBO control, irrespective of history of hypertension at Baseline.

7.5.5 Drug-Drug Interactions

As a biologic, CZP was not expected to exhibit the same potential for drug-drug interactions as small molecule agents. Immunoglobulins are not metabolized by the usual drug metabolism and conjugation enzyme systems, nor are immunoglobulins a substrate for membrane transporter mechanisms.

The potential for drug-drug interactions resulting from concomitant pharmacological effect could be possible, if co-administered with another drug with a similar mechanism of action. Formal drug-drug interaction studies were not performed other than the potential for PK drug-drug interaction between MTX and CZP. See the Clinical Pharmacology review by Christoffer Tornoe, PhD and Srikanth Nallani, PhD.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

See Section 7.3.5 Submission Specific Primary Safety Concerns for discussion of these data for the malignancies observed in the RA clinical development program.

7.6.2 Human Reproduction and Pregnancy Data

The use of CZP in pregnancy or lactating women has not been studied in clinical studies. As a result of unplanned pregnancies, there was limited data in the CZP RA studies safety database about CZP use and fetal outcomes. A total of 4 adult RA patients and 19 patients (all CZP indication studies) became pregnant in the CZP studies. Of the total 19 pregnancies, 6 resulted in live births, 5 full-term and 1 premature; 7 were terminated by elective abortion; 1 resulted in spontaneous abortion; 1 was a fetal death and 3 were ongoing at the time of this review. Overall, no congenital anomalies were observed in infants born to female patients who became pregnant while enrolled in a CZP study.

In addition, 8 female partners of male study patients (CZP treated) became pregnant while the male patient was enrolled in a CZP trial (all CZP indications). Seven of 8 pregnancies resulted in full term live births and 1 is ongoing, no additional information was submitted.

The current labeling for CIMZIA® specifies Pregnancy as Category B. There are, however, no adequate and well-controlled studies of CIMZIA in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

7.6.3 Pediatrics and Effect on Growth

There were no pediatric patients included in this BLA submission of CZP trials in patients with adult RA.

Request for Deferral of Pediatric Studies
The sponsor has submitted a Request for Deferral of Pediatric Studies for BLA 125271. The deferral request includes the ages of 4 to 17 years based on the diagnosis of juvenile rheumatoid arthritis (JRA). Biological agents in the treatment of JRA are uncommon in children less than 4 years of age. The sponsor planned to delay pediatric studies until after action is taken on the current RA submission (BLA 125271). It is noted that on February 19, 2002 during the End-of-Phase 2 meeting with CBER, the Agency agreed with UCBs development plan to request a written deferral of safety and efficacy data in pediatric patients. The sponsor has proposed to consult with the Agency in October 2008 for the projected plans to provide pediatric data to the Agency in 4th quarter 2010.

Given that currently there is one monoclonal anti-TNF antibody approved for JIA, the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) concurs with the agreement to study pediatric patients with JIA. The division will meet with the Pediatric Review Committee (PeRC) on September 24, 2008. The PeRC provides consultation on and general review of pediatric information submitted to the Agency in pediatric plans, assessments and studies conducted by sponsors and applicants pursuant to sections 505A and 505B to the Federal Food, Drug and Cosmetic Act (21 U.SC. 355a and 355c) to help ensure quality and consistency across the Agency. In addition, PeRC provides review of pediatric deferrals and waivers granted under section 505B of the Act.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There have been no reported accidental or intentional overdoses of CZP. The highest administered dose of CZP was 20mg/kg i.v. (Study 002) and 800 mg sc (Study 004). There did not appear to be dose-related safety issues.

7.7 Additional Submissions

120-Day Safety Update
The 120-Day Safety Update (120-DSU/DSU) included updated safety data from CZP in RA Phase 3 trials through the clinical data cutoff of August 31, 2007. The previous ISS clinical data cutoff was January 31, 2007. An additional 7 months of safety data were reported in the 120-DSU. CZP dose and administration (in PBO-controlled and OL trials) are summarized in **Table 1-DSU.** Data from Studies 027 and 050 showed no significant dose effect with regard to safety and efficacy to justify continuing OL studies with the 400 mg q2w dose regimen. Therefore, dosing for the OL studies was reduced to 200 mg sc q2w.

Table 1-DSU. 120-DSU: Dose and Administration Across PBO- and Open-Label RA Studies

Summary, Dose and Administration Across the CZP RA Studies		
Feeder Study, Dose and Administration	**OL Studies**	**Open-Label Study Dose and Administration**
Study 004, Panel 1: PBO or CZP 50, 100, 200 or 400 mg q4w (liquid)	**Study 004**	**Panel 1**: CZP 200 mg sc q4w, then post Amendment #4, CZP 400 mg sc q4w
Study 004, Panel 2: PBO or CZP 600 or 800 mg sc q4w (liquid)		**Panel 2**: CZP 400 mg sc q4w
Study 011: PBO or CZP 400 mg q4w. (monotherapy) (lyophilized)	**Study 015**	CZP 400 mg sc q4w + MTX
Study 014: PBO or CZP 400 mg sc q4w + MTX (lyophilized)		CZP 400 mg sc q4w + MTX
Study 027: PBO or CZP 200 mg sc q2w + MTX (lyophilized)	**Study 028**	CZP 400 mg sc q2w + MTX, then post Amendment 15Jul07, CZP 200 mg sc q2w + MTX
Study 027: PBO or CZP 400 mg sc q2w + MTX (lyophilized)		CZP 400 mg sc q2w + MTX, then post Amendment 15Jul07, CZP 200 mg sc q2w + MTX
Study 050: PBO or CZP 200 mg sc q2w + MTX (liquid)	**Study 051**	CZP 400 mg sc q2w + MTX, then post Amendment 15Jul07, CZP 200 mg sc q2w + MTX
Study 050: PBO or CZP 400 mg sc q2w + MTX (liquid)		CZP 400 mg sc q2w + MTX, then post amendment 15Jul07, CZP 200 mg sc q2w + MTX

Exposure

Based on additional safety data from OL studies, the clinical database cutoff date of August 31, 2007 was employed versus the clinical cutoff date of January 31, 2007. Total exposure included an additional 847 years for All CZP Doses (total of 4,065 pt-yrs); an additional 709 pt-yrs for CZP 400 mg q2w (total of 2,162 pt-yrs) and an additional 138 pt-yrs for CZP 400 mg q4w (total of 1,254 pt-yrs). See **Table 2-DSU**.

Table 2-DSU. Total Extent of Exposure in CZP RA Studies

120 Day Exposure Update CZP in RA Studies					
Studies 001, 002, 004, 011, 014, 015, 028, 050 and 051					
	PBO N=647	CZP 200 mg q2w + MTX N=640	CZP 400 mg q2w N=1487	CZP 400 mg q4w N=513	All CZP Doses N=2367
Duration of Exposure (days)					
Mean (SD)	127 (73)	226 (117)	531 (207)	893 (607)	627 (381)
Min., Max	14, 366	14, 369	14, 924	28, 1732	14, 1732
Total Exposure (Pt.-Yrs.)	225	396	2,162	1,254	4,065
Duration of Exposure					
< 6 months	597 (92%)	377 (59%)	116 (8%)	95 (19%)	321 (14%)
6 to < 12 months	8 (1%)	12 (2%)	93 (6%)	65 (13%)	243 0.3%)
12 to < 18 months	42 (7%)	251 (39%)	590 (40%)	46 (9%)	356 (15%)
18 to < 24 months	0	0	353 (24%)	25 (5%)	570 (24%)
24 to < 30 months	0	0	329 (22%)	14 (3%)	593 (25%)
30 to < 36 months	0	0	6 (0.4%)	8 (2%)	24 (1%)
36 to < 42 months	0	0	0	27 (5%)	27 (1%)
42 to < 48 months	0	0	0	88 (17%)	88 (4%)
≥ 48 months	0	0	0	145 (28%)	145 (6%)
≥ 12 months	42 (7%)	251 (39%)	1278 (86%)	353 (69%)	1803 (76%)

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Exposure and Demographic Characteristics

The global population demographic characteristics in the OL studies were consistent with the randomized, double-blind portion of CZP RA studies. The majority of participants were female and Caucasian and most patients ≥ 18 to < 64 years of age. See **Table 3-DSU.**

Table 3-DSU. Duration of Exposure by Age (18 to < 64 years compared to ≥ 65 years)

120-DSU: Exposure and Age of Patients			
Parameter	CZP 400 mg q2w N = 1487	CZP 400 mg q4w N = 513	All CZP Doses N = 2367
Total (Pt.-Yrs.)	2162	1254	4065
Age: 18 to < 64 years			
	N = 1281	N = 428	N = 2018
Mean (SD)	537 (201)	889 (614)	631 (377)
Median (min., max)	504 (14, 924)	1130 (28, 1732)	616 (14, 1732)
Total (Pt.-Yrs.)	1884	1042	3488
Age: ≥ 65 years			
	206	85	349
Mean (SD)	494 (234)	913 (572)	604 (398)
Median (min., max)	489 (14, 896)	1148 (28, 1713)	602 (14, 1713)
Total (Pt.-Yrs.)	278	213	577

Overall Deaths in the CZP RA Program

There were 4 deaths reported since the ISS clinical cutoff 31January2007 and 2 additional deaths reported between 15Jul2007 and 30Nov2007. The 4 additional deaths include 3 deaths secondary to infection (sepsis, Staphylococcal pneumonia and pulmonary tuberculosis) and one death secondary to a malignant neoplasm (gastric cancer). These deaths were similar in etiology to those seen previously.

In summary, there were a total of 35 deaths were reported (versus 33 reported by sponsor) across the CZP RA program. A total of 4 of these 35 deaths (CZP 400 mg q2w treatment) occurred before the safety cut-off of 15Jul2007 and 2 of these 35 deaths (Pt. #51077/141044, Study 015 and Pt. #223/003, Study 028) occurred in the interval between the clinical cutoff 31Aug2007 and the safety cutoff 30Nov2007. These two deaths account for reported differences in the total number of deaths (23 versus 25) in OL studies. See **Table 4-DSU.** Patient narratives appear below.

There were two deaths in which the final adjudication for the cause of death was different from that reported by the sponsor: Pt. # 114/021 in Study 028, the cause of death was considered to be staphylococcal pneumonia rather than cardiac failure; and Pt. #603/0009 in Study 051, the cause of death was considered to be sepsis rather than cardiogenic shock.

Table 4-DSU. Deaths in OL Studies Reported (120-DSU, through November 1, 2007)

Deaths: Open-label Studies through August 31, 2007 (inclusive as known on November 1, 2007)				
CZP Treatment Group Study Site/ Pt. # (Study #) Country	Age/ Sex/R	Event Onset (dys) from 1st Inject.	 Prev. Inject.	 Cause of Death
PBO + MTX / 400 sc q2w; N=857				
(b.) 215/004 (Study 028) Ukraine	63/F/C	545 days	27 days	Neoplasm, Gastric Cancer
400 sc q2w + MTX / 400 sc q2w + MTX; N=857				
(b.) 114/021 (Study 028) Serbia, Montenegro	55/F/C	676 days	67 days	Pneumonia staphylococcal
061/036 (Study 028) Czech Republic	76/F/C	217 days	48 days	Pulmonary Tuberculosis
51077/141044 (Study 028)	73/F/C			Heart Failure
PBO + MTX / 400 sc q2w + MTX; N=857				
(b.) 011/014 (Study 028) Argentina	48/F/C	487 days	42 days	Neoplasm malignant
200 sc q2w + MTX / 400 sc q2w + MTX; N=582				
603/009 (Study 051) Czech Republic	57/F/C	314 days	34 days	Sepsis

Narratives: Four additional deaths reported through 15Jul2007.

Patient #215/004 (PBO + MTX/400 mg q2w) was a 63-year old Ukrainian female with a medical history of RA, arterial hypertension and pulmonary fibrosis. Concomitant medications included MTX, prednisolone, diclofencac, enalepril and indapamide. Chest x-ray during Study 027 showed pneumosclerosis with calcification at fibrous roots. PPD was reportedly negative yet reactive between 1-5mm in diameter. Following a year-and-a-half of exposure to CZP, gastric polyps and Stage IV stomach cancer was diagnosed. Following hospitalization with gastralgia, fever and gastroduoendoscopy, pathology showed low-grade differentiated adenocarcinoma. Chemotherapy was initiated and the patient died two months later. The cause of death was attributed to stomach cancer and exposure to CZP cannot be excluded as contributing to the cancer.

Patient #114/021 (400 mg q2w + MTX/400 mg q2w + MTX) was a 55-year old Serbian female with a medical history of hypertension, unspecified psychiatric symptoms and status-post ovarian cystectomy. Concomitant medications included MTX, prenisolone, diclofencac, metoprolol and atenolol. She developed influenza-lie symptoms with fever, fatigue and cough and reported blood in her stools and was hospitalized for suspected tuberculosis abscess on a chest x-ray showing empyema and pneumonia. A pleural puncture sample was positive for *Staphylococcus aureus* and negative for mycobacterium. She was treated with clindamycin, amikacin and ceftazidine. Ciprofloxacin and vancomycin were initiated and amikacin and ceftazidine were discontinued. She remained febrile and was transferred to another hospital for treatment. Her chest x-ray showed bilateral infiltrations and sputum cultures were positive for *Pseudomonas aeruginosa* and *Staphylococcus aureus.* Treatment was changed to piperacillin, tazobactam, ciprofloxacin, vancomycin and unspecified antifungal and cardiac medications. She deteriorated and echocardiogram showed a left ventricular ejection fraction of 30% with a posterior pericardial effusion. She became unresponsive and died. Causality was attributed to *Pseudomonas aeruginosa* and *Staphylococcus aureus* pneumonia and, possibly, was related to exposure to CZP.

Patient #011/014 (PBO + MTX/400 mg q2w + MTX) was a 50-year old Argentinian female with a medical history of obesity, diabetes mellitus, ateriosclerosis, hypothyroidism, glomerulonephritis and osteoarthritis of the knee. Concomitant medications included MTX,

quinine sulfate, metformin, levothyroxine, enalapril, deflazacort and clonazepam. She was started on PBO + MTX in Study 027. She developed hypertension and dyspepsia due to biliary lithiasis associated with elevated bilirubin (3.6 mg/dL, normal range 0.2-1.2 mg/dL) and elevated GGT. She was treated with enalapril and these abnormalities resolved. She developed worsening hypochondrium pain and was hospitalized. Chest x-ray showed pleural effusion and ultrasound was consistent with ascites without apparent abnormality of the liver, spleen or ovaries. Broad spectrum antibiotics and heparin as well as unspecified beta-blockers were initiated. She was discharged and readmitted with recurrent abdominal pain, dyspnea and lower extremity edema. Throacentesis showed malignant neoplastic cells of unknown origin, her condition deteriorated and she died. No autopsy was performed. Cause of death was attributed to the malignant neoplasm. Exposure to CZP could not be excluded due to the malignant neoplasm.

Patient #061/036 (400 mg q2w + MTX /400 mg q2w + MTX) was a 76-year old Czech female with a history of diabetes mellitus, venous insufficiency and hypertension. She had a screening chest X-ray which showed fibrous changes and a PPD with induration of 9mm which was considered normal due to prior BCG vaccination. She was hospitalized with severe pancytopenia and fever, and CT showed bilateral lung micronodulation. *Mycobaterium tubercu- losis* was confirmed by positive sputum microscopy on culture. She developed senile marasmus with cerebral arteriosclerosis. Autopsy was consistent with pulmonary TB and atherosclerosis. Cause of death was pulmonary TB and most likely attributed to exposure to CZP.

Narratives: Two additional deaths were reported between 15Jul2007 and 30Nov2007.

Pt. #51077/141044 (400 mg q4w/ 400 mg q2w) was a 73-year old female with no relevant history except RA experienced hospitalization due to dyspnea and was diagnosed with heart failure including an anterior wall myocardial infarction (MI). Blood tests confirmed MI. These events occurred 52 days following the last dose of CZP 400 mg (1659 days after the first CZP dose). She had ventricular fibrillation with cardiopulmonary arrest and died. Causality to the study product could not be excluded.

Pt. #223/003 (400 mg q2w + MTX/ 400 mg q2w + MTX) was 70-year old male with history of euthyroid multi-nodular goiter, chronic non-ulcer colitis, RA, duodenal ulcer and essential hypertension. He experienced deep vein thrombosis and mild pulmonary embolism which reportedly resolved. He later developed dyspnea, pleurisy and a chest x-ray with pleural effusion (positive for TB by culture) and died. Causality elated to tuberculosis infection cannot be excluded as the primary cause of death.

Withdrawals
An additional 43 patients with AEs leading to withdrawal were reported in the 120-DSU as shown in **Table 5-DSU.** The AEs leading to withdrawal were similar in type and frequency to what was observed previously. See **Table 6-DSU.**

Table 5-DSU. Cumulative Summary of AEs and AEs Leading to Withdrawal

120-DSU: Cumulative Summary of AEs and AEs Leading to Withdrawal		
	All CZP Doses Cut-off 31Jan2007	**All CZP Doses (120DSU)** Cut-off 31Aug2007
Total Exposure, Pt.-Yrs.	**3218**	**4065**
Any AE	1934 (82%)	2037 (86%)
Rate [a]	418	386
Incidence per 100 pt.yrs [b]	200	183
Serious AEs	523 (22%)	616 (26%)
AEs Leading to Death	28 (1.2%)	32 (1.4%)
AEs Leading to Withdrawal [c.]	N = 2013 202 (10%)	N = 2013 245 (12%)

(a) Rate was calculated as (total # of events/total exposure in years) x 100;
(b) Incidence per 100 pt.-yrs was calculated as (total # pts. experiencing AE of interest /total durations up to the first occurrence of AE of interest for patients with that AE and the total study duration for patients not experiencing that AE) x 100.
(c.) Due to the CRF design, the AEs leading to withdrawal from Studies 002 and 004 were not included; percentages were calculated for the subpopulation excluding these studies.
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Table 6-DSU. Cumulative AEs Leading to Withdrawal in ≥ 0.3% of Patients – CZP in RA

Cumulative Adverse Events Leading to Withdrawal ≥ 0.3% by SOC, HLT, PT Studies 001, 011, 014, 015, 027, 028, 050 and 051				
	All CZP Doses ISS (31Jan2007) N = 2013		**All CZP Doses** 120-DSU (31Aug2007) N = 2013	
	n (%)	100 pt.-yrs.	n (%)	100 pt.-yrs.
# Pts with AEs Leading to Withdrawal	202 (10%)	6.95	245 (12%)	6.52
Blood and lymphatic system disorders	10 (0.5%)	0.34	11 (0.5%)	0.29
Cardiac disorders	19 (0.9%)	0.64	19 (0.9%)	0.5
Gastrointestinal disorders	8 (0.4%)	0.27	8 (0.4%)	0.21
General disorders, administr. site condit.	14 (0.7%)	0.47	14 (0.7%)	0.37
Infections and infestations	73 (3.6%)	2.48	92 (4.6%)	2.42
Injury, poison., procedure, complications	10 (0.5%)	0.34	10 (0.5%)	0.26
Investigations	5 (0.2%)	0.17	9 (0.4%)	0.24
Musculoskeletal, CTD disorders	17 (0.8%)	0.58	18 (0.9%)	0.47
Neoplasms benign, malignant, unspecif.	20 (1%)	0.68	30 (1.5%)	0.79
Nervous system disorders	9 (0.4%)	0.3	9 (0.4%)	0.24
Reproductive system, breast disorders	5 (0.2%)	0.17	6 (0.3%)	0.16
Respiratory, thoracic, mediastin. disor.	7 (0.3%)	0.24	10 (0.5%)	0.26
Skin, subcutaneous tissue disorders	24 (1.2%)	0.81	25 (1.2%)	0.66
Vascular disorders	5 (0.2%)	0.17	7 (0.3%)	0.18

Revised from sponsor Table 2.7.4:6, page 27 of 77, 120-DSU.

Serious Adverse Events

An additional 93 SAEs were reported in the 120-DSU since the ISS clinical cutoff, 31Jan2007. A total of 523 SAEs (22% of pts.) in the ISS (n=2367) versus 616 SAEs (26% of pts.) in the 120-DSU (n=2367) based on these additional 93 SAEs. See **Table 7-DSU.** Overall, the SAEs were similar in type and incidence to what was reported in the ISS..

Table 7-DSU. Cumulative SAEs by SOC and HLT, Incidence ≥ 0.5% in the ISS or 120-DSU

Serious Adverse Events by SOC, HLT with Incidence ≥ 0.5% in ISS or 120-DSU				
Studies 001, 002, 004, 011, 014, 015, 027, 028, 050, 051				
	All CZP Doses ISS (31Jan2007) N =2367		All CZP Doses 120-DSU (31Aug2007) N = 2367	
SOC, *HLT*	n (%)	100 pt.-yrs.	n (%)	100 pt.-yrs.
Total Exposure, Pt.-Yrs.	3218		4065	
Total # pts. w/SAEs	523 (22%)	17.88	616 (26%)	16.98
Blood and lymphatic system disorders	16 (0.7%)	0.49	19 (0.8%)	0.46
Cardiac disorders	53 (2%)	1.63	59 (3%)	1.44
Gastrointestinal disorders	32 (1.4%)	0.98	40 (2%)	0.97
General disorders, administr. site condit.	23 (1%)	0.7	25 (1%)	0.61
Hepatobiliary disorders	19 (0.8%)	0.58	21 (0.9%)	0.51
Cholecytitis, cholelithiasis	15 (0.6%)	0.46	17 (0.7%)	0.41
Infections and Infestations	172 (7.3%)	5.39	211 (8.9%)	5.26
Lower respiratory tract and lung infect.	39 (1.6%)	1.19	52 (2.2%)	1.26
Tuberculosis infections	23 (1%)	0.67	30 (1.3%)	0.7
Bacterial infections NEC	19 (0.8%)	0.58	24 (1%)	0.58
Upper respiratory tract infections	16 (0.7%)	0.49	18 (0.8%)	0.44
Urinary tract ifnections	15 (0.6%)	0.46	19 (0.8%)	0.46
Skin structures, soft tissue infections	7 (0.3%)	0.21	12 (0.5%)	0.29
Injury, poisoning, procedural complications	52 (2.2%)	1.6	63 (2.7%)	1.54
Investigations	12 (0.5%)	0.37	13 (0.5%)	0.31
Musculoskeletal, connective tissue disord.	118 (5%)	3.7	141 (6%)	3.52
Neoplasms benign, malignant, unspecified	32 (1.4%)	0.98	50 (2.1%)	1.24
Nervous system disorders	30 (1.3%)	0.92	31 (1.3%)	0.75
Reproductive system, breast disorders	15 (0.6%)	0.46	24 (1%)	0.58
Skin, subcutaneous tissue disorders	10 (0.4%)	0.3	11 (0.5%)	0.27
Vascular disorders	27 (1.1%)	0.83	33 (1.4%)	0.8
Peripheral embolism, thrombosis	10 (0.4%)	0.31	14 (0.6%)	0.34

Revised from sponsor Table 2.7.4:5, page 24 of 77, 120-DSU.

Malignancy

The types of malignancies reported in the 120-DSU were similar to those reported in the general CZP RA population and those reported with other TNF-inhibitor agents. See **Table 8-DSU.**

Table 8-DSU. Additional SAE Malignancies Reported in the 120-DSU

Additional Malignancies in 120-DSU (cutoff 31Aug2007)				
Pt. #, Study #, Age	**PT/ Verbatium**	**CZP Treatment**	**Exposure (days) from 1st, most recent dose**	**Outcome; Final Action**
Skin Neoplasms				
50815/141046, 76yrs. Study 015	Basal cell carcinoma/ nasal Nasal leison basocellular carcinoma	400 mg sc q4w + MTX	1344, 0	Resolved, None
192/001, 64 yrs. Study 028	Squamous cell carcinoma/ left temploral squamous cell carcinoma	400 mg sc q2w + MTX	770, 1	Resolved;. Pt. withdrawn
Gastrointestinal				
114/010, 73 yrs. Study 028	colon cancer/ colon cancer (adenocarcinoma invasum)	400 mg sc q2w + MTX	686, 0	Ongoing ca.; Withdrawn
Respiratory Tract Neoplasm				
76/002, 49 yrs. Study 028	Lung neoplasm/ Multiple nodes on bilateral lungs	400 mg sc q2w + MTX	730, 1	Ongoing, Withdrawn
Reproductive System Neoplasms				
194/0002, 52 yrs. Study 051	Breast cancer/ Interductal carcinoma of left breast	400 mg sc q2w + MTX	61, 3	Ongoing, Withdrawal

Revised from sponsor Table 2.7.4:11, page 36 of 77, 120-DSU

Infections

A total of 39 patients had infectious SAEs. The infectious SAEs were similar in type and incidence as those reported in the original ISS. See **Table 9-DSU.**

Table 9-DSU. Cumulative SAEs, Infections/Infestations (HLT) ≥ 0.5% in the ISS and 120-DSU

SAEs Infections and Infestations (HLT) Incidence ≥ 0.5 in ISS or 120-DSU				
Studies 001, 002, 004, 011, 014, 015, 027, 028, 050 and 051				
	All CZP Doses ISS (31Jan2007) N = 2367		All CZP Doses 120-DSU (31Aug2007) N= 2367	
Total Exposure in Pt.-Yrs.	3218 pt.-yrs.		4065 pt.-yrs.	
SOC, HLT	n (%)	100 pt.-yrs.	n (%)	100 pt.-yrs.
SAEs, Infections and Infestations	172 (7.3%)	5.39	211 (8.9%)	5.26
Tuberculosis	23 (1%)	0.67	30 (1.3%)	0.7
Abdominal, GI infections	7 (0.3%)	0.21	7 (0.3%)	0.17
Lower respirat. tr., lung infect.	39 (1.6%)	1.19	52 (2.2%)	1.26
Bacterial infections NEC	19 (0.8%)	0.58	24 (1%)	0.58
Skin structure, soft tiss. infect.	7 (0.3%)	0.21	12 (0.5%)	0.29
Upper respirat. tract infections	16 (0.7%)	0.49	18 (0.8%)	0.44
Urinary tract infections	15 (0.6%)	0.46	19 (0.8%)	0.46
Infections NEC	11 (0.5%)	0.34	12 (0.5%)	0.29
Sepsis, bacteremia, viremia	11 (0.5%)	0.34	11 (0.5%)	0.27
Streptococcal infections	9 (0.4%)	0.27	11 (0.5%)	0.27

Revised from sponsor Table 2.7.4:9, page 31 of 77, 120-DSU

Tuberculosis

A total of 23 TB cases were reported in the ISS and 6 new cases were reported in the 120-DSU (cutoff July 15, 2007; see **Table 10-DSU**) and 4 additional cases (through August 31, 2007). A total of 33 TB cases in 31 patients were reported across the CZP RA studies [23 cases (ISS) and 10 newly reported since ISS cutoff through August 31, 2007]. These results were consistent with TB reported in the ISS.

Table 10-DSU. Summary of Additional Tuberculosis Events in 120-DSU (as of 31August2007)

6 Additional Cases of Tuberculosis in 120-DSU (cutoff 31August 2008)					
Pt #, Study #, Country, Age	CZP Tx, con Concomit. Meds	Baseline PPD, CXR	Exposure (dy	TB confirmation	Outcome, ongoing
52/005, Study 028, Croatia, 76y/F	400 mg sc q2w + MTX	PPD 16-20 mm CXR reticular fibrosis	805	Quantiferon test	ongoing
61/036, Study 028, Czech Repub., 77y/F	400 mg sc q2w + MTX	Neg. (9mm), CXP light fibrosis	531	Culture	Death, pulmonary TB
109/004, Study 028, Russia, 52 y/F	400 mg sc q2w + MTX	Neg. (6-10mm)	756	Unknown	Ongoing
102/0008, Study 051, Lithuania, 55 y/F	400 mg sc q2w +MTX, methylprednisolone	No reaction, CXPR neg.	295	Culture	pul TB, TB pleurisy recovered
56721/111208, Study 015, Czech Repub., 58y/F	400 mg sc q4w + MTX, methylprednisolone	Reaction (16-20mm) CXR pos. but not "clinically significant"	1,111	Biopsy	Ongoing
111/021, Study 028, Russia, 55y/F	400 mg sc q2w + MTX, methylprednisolone	3 mm, CXR normal	700	Unknown	Ongoing

Revised from sponsor Table 2.7.4:10, page 33 of 77, 120-DSU.

Congestive Heart Failure
An additional 3 patients reported Congestive Heart Failure TEAEs in the All CZP Doses group (since the ISS) for a cumulative total of 9 patients with Congestive Heart Failure TEAE across the CZP RA program.
- Cardiac Failure TEAEs were similar across the ISS versus the 120-DSU (0.3%, 0.18 per 100 pt-yrs) versus (0.4%, 0.22 per 100 pt-yrs). One patient (Pt. #114/021 in Study 028) had a new SAE of cardiac failure (120-DSU). She died most likely secondary to infection. See the narrative in *Section 7.3.1 Deaths* in this review.
- A total of 10 patients with SAEs of (HLT) Heart failure, including (PT) Cardiac failure, cardiopulmonary failure and Congestive heart failure were reported in the ISS.
- No new (HLT) Heart failure SAEs were reported in the 120-DSU from August 31 through November 31, 2007.
Overall, these data suggest that longer exposure to CZP did not meaningfully increase the risk of CHF.

Hepatic Events
A total of 1814 out of 2367 patients (77%) in the All CZP Doses group received concomitant MTX which is known to be hepatotoxic.
- 2 additional SAEs were reported (120-DSU) in the (SOC) Hepatobiliary disorders both within the HLT cholecystitis and cholelithiasis.
- No additional patients were reported with SAEs Liver Function analyses, Cirrhosis or Ascites in the 120-DSU.
- A total of 3 new SAEs Hepatic events were reported (120-DSU cutoff of 31Aug2007 through 30Nov2007). The first case was Pt # 222/003 in Study 028) who had Cholecystitis. The second case was Pt. #600/005 in Study 051 who experienced Cholecystitis acute. The third case was Pt. #101/001 in Study 051 had Hepatitis.

Overall, there did not appear to be a signal for clinical hepatotoxicity in the 120-DSU.

Hematology
- Two new hematological SAEs were reported since the ISS. Few serious hematological events were reported in either the ISS or 120-DSU.

Pancytopenia
- 1 case (Pt. # 61/036 in Study 028) had an SAE of Pancytopenia (120-DSU). This patient died secondary to TB.
- 2 patients with SAE of Pancytopenia (0.1%; 0.06 per 100 pt-yrs) were reported in the ISS.

Cumulatively, there were 3 patients with the SAE of pancytopenia in the CZP RA program (0.1%; 0.07/100 pt-yrs). In the current CIMZIA® labeling, in the WARNINGS AND PRECAUTIONS section, in the subsection, Hematological Reactions, rare reports of pancytopenia are reported with TNF inhibitors.

Leucopenia
-One SAE of leucopenia (Pt. # 120/027 in Study 051, 120-DSU between 31Aug2007 and 30Nov2007) was experienced by a 55 year old female, 533 days from the first CZP dose 400 mg sc q2w and 14 days from the last CZP dose, 400 mg q2w. Concomitant medications included MTX, naproxen, methylprednisolone, pantoprazole and levothyroxine. The lowest WBC count was 3.13 x 10(3) and it was resolved in 4 weeks.

Overall, the incidence of TEAEs Hematological events (HLT) was similar in the ISS compared to the 120-DSU. See **Table 11-DSU**.

Table 11-DSU. Cumulative Hematological TEAEs (HLT), Incidence ≥ 0.55%, ISS or 120-DSU

Cumulative Hematology TEAEs by HLT, Incidence ≥ 0.5% in ISS or 120-DSU				
Studies 001, 002, 004, 011, 014, 015, 027, 028, 050, 051				
SOC / HLT	All CZP Doses ISS (31January2007)		All CZP Doses 120-DSU (31August2007)	
Total Exposure, Pt.-Yrs.	3218 pt.-yrs.		4065 pt.-yrs.	
	n (%)	100 pt.-yrs.	n (%)	100 pt.-yrs.
Blood and lymphatic system disorders				
Eosinophilic disorders	36 (1.5%)	1.11	39 (1.6%)	0.95
Anemias NEC	61 (2.6%)	1.89	76 (3.2%)	1.87
Leukocytes NEC	28 (1.2%)	0.86	29 (1.2%)	0.71
Leukopenias NEC	24 (1%)	0.74	29 (1.2%)	0.7
Investigations				
Coagulation, bleeding analyses	43 (1.80%)	1.32	54 (2.3%)	1.32
White blood cell analyses	37 (1.6%)	1.14	43 (1.8%)	1.05

Coagulation Abnormalities
As explained by the sponsor, extensive testing of the effect of CZP or its components (antigen binding fragment [Fab'], or PEG) on coagulation assays was performed by independent experts at the (b) (4). Testing included evaluation of the aPTT, Prothrombin (PT), dilute Russell's viper venom time (dRVVT), silica clotting time, thrombin time (TT), and thrombin generation.

Overall, the conclusion from these investigations is that CZP or PEG interferes with some commercial assays to measure aPTT, including specific assays which were used in the clinical trials under review. The effect is related to interference by CZP and PEG with the phospholipid component of the assays. The interference is an *in vitro* phenomenon and there appears to be no evidence for an effect on *in vivo* coagulation function.

Analysis conducted after the ISS was submitted to the Agency showed that the studies differed in the assay kit used to measure aPTT. Studies 050 and 051 used the HemosIL APTT-SP liquid test while Studies 011, 014, and 015 used the Dade Actin, Fisher Diagnostics APTT-LS, and HemosIL SynthASil test kits, respectively.

In summary, no association between bleeding and reports of abnormal coagulation assays was demonstrated. Increases in the aPTT were only seen when aPTT was assayed using the Hemosil aPTT-SP kit and not with the Dade Actin, Fisher Diagnostics APTT-LS, or HemosIL SynthASil APTT test kits. The incidence of bleeding AEs (combined terms) and the incidence in the All

Doses group were similar in the 120-DSU versus the corrected ISS. Based on this safety database review, prolongation of clotting time may most likely be attributed to a laboratory abnormality due to interference by CZP and PEG on the assay in the some kits.

Injection Site Reactions
Overall, there was no change in the incidence of injection site reactions with increased exposure to CZP in patients with RA.

Auto-antibodies
There were no new SAEs of lupus-like illness in the 120-DSU.

Significant Adverse Event of Interest
Infections
Rates of various infections were similar when data from the 120-DSU were added to the safety database. See **Table 12-DSU.**

Table 12-DSU. AEs, Infections and Infestations (HLT), Incidence ≥ 2%, ISS or 120-DSU

AEs Infections and Infestations (HLT) Incidence ≥ 2% in ISS or 120-DSU				
Studies 001, 002, 004, 011, 014, 015, 027, 028, 050 and 051				
	All CZP Doses ISS (31Jan2007) N = 2367		All CZP Doses 120-DSU (31Aug2007) N= 2367	
Total Exposure in Pt.-Yrs.	3218 pt.-yrs.		4065 pt.-yrs.	
	n (%)	100 pt.-yrs.	n (%)	100 pt.-yrs.
Any AE, Infections and Infestations SOC	1313 (56%)	70.55	1448 (61%)	65.77
Upper respiratory tract infections	695 (29%)	28	784 (33%)	26
Urinary tract infections	261 (11%)	8.6	306 (13%)	8.1
Lower respiratory tract, lung infection	272 (12%)	8.97	326 (14%)	8.6
Bacterial infections NEC	115 (4.9%)	3.61	130 (5.5%)	3.26
Viral infections NEC	117 (4.9%)	3.67	150 (6.3%)	3.76
Herpes viral infections	161 (6.8%)	5.15	188 (7.9%)	4.79
Infections NEC	104 (4.4%)	3.26	120 (5.1%)	2.99
Influenza viral infections	79 (3.3%)	2.47	108 (4.6%)	2.69
Skin structure, soft tissue infections	78 (3.3%)	2.43	97 (4.1%)	2.4
Ear infections	43 (1.8%)	1.33	53 (2.2%)	1.3
Dental, oral soft tissue infections	77 (.3%)	2.4	90 (3.8%)	2.23
Abdominal , GI infections	56 (2.4%)	1.73	69 (2.9%)	1.7
Fungal infections NEC	60 (2.5%)	1.86	72 (3%)	1.78

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Markedly Abnormal Shifts (Grade 3 or 4)
Overall, the percentages of patients with markedly abnormal (Grade 3 or 4) hemoglobin shifts and white blood cell (WBC) indices values, ISS versus 120-DSU, did not show a meaningful difference. See **Table 13-DSU.**

Table 13-DSU. Markedly Abnormal (Grade 3 or 4) Hematology Values, ISS vs 120-DSU

Summary: Shift Table for Markedly Abnormal (Grade 3 or 4) Hematology Values								
		Any (PBO included) / All CZP Doses ISS (31Jan2007)/ 120-DSU (31Aug2007)						
		Baseline, (n (%)						
Parameter	Worst Grade During Study	N	Low		Normal		High	
			ISS	120-DSU	ISS	120-DSU	ISS	120-DSU
Hgb	Low Grade 4	2113	3 (0%)	3 (0%)	0	0	0	0
	Low Grade 3	2113	133 (0.6%)	17 (0.8%)	3 (0.1%)	4 (.2%)	0	0
WBC	Low Grade 4	2113	0	0	0	0	0	0
	Low Grade 3	2113	0	0	1 (0%)	2 (0.1%)	0	0
Neutrophils	Low Grade 4	2113	0	0	1 (0%)	1 (0%)	0	1 (0%)
	Low Grade 3	2113	1 (0%)	1 (0%)	16 (0.8%)	19 (0.9%)	2 (0.1%)	2 (0.1%)
Lymphocytes	Low Grade 4	2113	0	0	1 (0%)	1 (0%)	0	0
	Low Grade 3	2113	17 (0.8%)	19 (0.9%)	9 (0.4%)	9 (0.4%)	0	0
Platelets	Low Grade 4	2113	0	0	2 (0.1%)	2 (0.1%)	1 (0%)	1 (0%)
	Low Grade 3	2113	0	0	0	0	0	0
aPTT	High Grade 3	969	18 (1.9%)	21 (2.2%)	66 (6.8%)	91 (9.4%)	16 (1.7%)	18 (1.9%)
PT	High Grade 3	969	0	0	17 (1.8%)	19 (2%)	4 (0.4%)	4 (0.4%)
INR	High Grade 3	567	0	0	11 (1.9%)	13 (2.3%)	3 (0.5%)	3 (0.5%)

Liver Function Tests and Other Chemistry Tests

The percentages of patients with markedly abnormal (Grade 3 or 4) asparate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT) and alkaline phosphatase, and total calcium, glucose, electrolytes, albumin, total protein, and creatinine shifts were similar across the ISS and the 120-DSU.

Common Adverse Events

When adjusted for differing durations of exposure, the rates of common adverse events were similar when the data from the 120-DSU were added to the safety database. See **Table 14-DSU.** The most common AEs (PT) in the 120-DSU were nasopharyngitis, rheumatoid arthritis, upper respiratory tract infection, urinary tract infection and headache. These AEs were consistent with those most commonly reported in the ISS.

Table 14-DSU. AEs by PT, Incidence ≥ 3% in All CZP Doses Group by # Pts. /100 pt-yrs

All Common AEs by PT, Incidence ≥ 3% in All CZP Doses				
	All CZP Doses ISS (31Jan2007)		All CZP Doses 120-DSU (31August2007)	
	n (%)	100 pt.-yrs.	n (%)	100 pt.-yrs.
Total Exposure in Pt.-Yrs.	3218		4065	
Nasophyarngitis	280 (11.8%)	9.59	307 (13%)	8.36
Rheumatoid arthritis	266 (11.2%)	8.69	302 (12.8%)	7.83
Upper respiratory tr. infection	214 (9%)	7.03	255 (10.8%)	6.7
Urinary tract infection	205 (8.7%)	6.64	238 (10.1%)	6.17
Headache	219 (9.3%)	7.31	230 (9.7%)	6.08
Hypertension	189 (8%)	6.09	218 (9.2%)	5.62
Back pain	166 (7%)	5.35	191 (8.1%)	4.91
Rash	141 (6%)	4.5	156 (6.6%)	3.96
Cough	130 (5.5%)	4.16	140 (5.9%)	3.56
Diarrhea	127 (5.4%)	4.05	140 (5.9%)	3.54
Sinusitis	114 (4.8%)	3.63	135 (5.7%)	3.41
Herpes simplex	111 (4.7%)	3.51	130 (5.5%)	3.27
Arthralgia	112 (4.7%)	3.54	129 (5.4%)	3.24
Bronchitis	99 (4.2%)	3.12	120 (5.1%)	3.01
Nausea	114 (4.8%)	3.61	119 (5%)	2.99
Bronchtis acute	96 (4.1%)	2.99	116 (4.9%)	2.89
Influenza	79 (3.3%)	2.47	108 (4.6%)	2.69
Phayngitis	85 (3.6%)	2.65	104 (4.4%)	2.69
Dyspepsia	88 (3.7%)	2.77	100 (4.2%)	2.5
Pyrexia	89 (3.8%)	2.77	95 (4%)	2.35
ALT	81 (3.4%)	2.53	92 (3.9%)	2.29
Pharyngolaryngeal pain	77 (3.3%)	2.41	83 (3.5%)	2.06
Dizziness	73 (3.1%)	2.28	80 (3.4%)	1.98
Rhinitis	70 (3%)	2.17	80 (3.4%)	1.98
Vomiting	70 (3%)	2.18	79 (3.3%)	1.95
Edema peripheral	71 (3%)	2.21	76 (3.2%)	1.88
Anemia	61 (2.6%)	1.89	76 (3.2%)	1.87
Abdominal pain upper	68 (2.9%)	2.12	75 (3.2%)	1.85
Pain in extremity	68 (2.9%)	2.12	75 (3.2%)	1.85
Abdominal pain	58 (2.5%)	1.79	70 (3%)	1.72
Insomnia	58 (2.5%)	1.8	70 (3%)	1.72

Revised form sponsor Table 2.7.4:7, page 28 of 77, 120-DSU

Self-Injection of CZP Using a Prefilled Syringe: Substudy 051

A patient's ability to self-inject CZP using a PFS was assessed in Substudy 051. This Substudy was conducted after the clinical cutoff date (31January2007, ISS).

- 91 patients enrolled (Substudy 051);
- 14 patients (15%) reported 16 TEAEs during the 3 self-administration visits.
- 9 different patients (10%) reported TEAEs during the 3 visits before self-administration.
- No TEAEs of acute hypersensitivity reactions (event within 2 hours of injection) were observed.
- Bronchitis acute was the only AE reported by 1 patient before and during the self-administration.

In summary, no trend of TEAEs was observed during the assessment of self-injection of CZP using a PFS (Substudy 051).

Overall Conclusions from 120-DSU

In conclusion, the data from the120-DSU did not reveal any new safety concerns beyond those identified in the ISS.

8 Postmarketing Experience

CIMZIA® is commercially available in Switzerland as of January 3, 2008 for patients with Crohn's Disease following the approval by the Swiss health authority (Swissmedic) on September 7, 2007.

CIMZIA® was approved as a new molecular entity (BLA 125160) by the Food and Drug Administration (Division of Gastroenterology Products) April 30, 2008 for the indication of the treatment of moderately to severely active Crohn's Disease. The labeling reflects the Dose and Administration for Crohn's Disease as 400 mg initially and at Weeks 2 and 4. If response occurs, follow with 400 mg every four week. Because these approvals occurred recently, no post-marketing data are available.

9 Appendices

9.1 Literature Review/References

The literature references are cited in the Sections of this review in which the reference was noted.

9.2 Labeling Recommendations

The first labeling meeting is scheduled for August 19, 2008 which is after the required signature date (August 13, 2008) for this Medical Officer review of BLA 126271.

In brief overview, the labeling should reflect the following new clinical information based on this submission:
1. The magnitude of the safety signal for infections, including the higher risk for tuberculosis, as well as the observation of higher incidence of tuberculosis in Eastern European countries;
2. The slightly lower treatment effect (as measured by the primary efficacy endpoint, the ACR20 response at 24 weeks) observed with the proposed alternate monotherapy (CZP 400 mg q4w without a preceding loading dose regimen);
3. The higher rate of anti-CZP antibody development in CZP 200 gm q2w dose regimen and the observed trend for decreased efficacy as measured by the ACR20 response;
4. The risk of development of lymphoma with CZP treatment; and
5. The risk of abnormal coagulation test results, specifically the activated prothrombin time (aPTT) with concomitant CZP. There appears to be interference with the human clinical assay for aPTT without a clinical risk of bleeding diatheses with CZP treatment.

9.3 Advisory Committee Meeting

Currently, there are three TNF blockers approved for adult patients with RA. The safety and efficacy results for CZP are similar to those of the approved products. The division determined

that the data submitted were adequate to make a decision on an action without consulting an Arthritis Advisory Committee.

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2008.002.A.00007
APPLICATION NUMBER	BLA 125271
LETTER DATE	12-06-2007
REQUESTED DUE DATE	08-01-2008
PDUFA DATE	October 3, 2008
DATE OF CONSULT REQUEST	January 15, 2008
REVIEW DIVISION	DAARP
MEDICAL REVIEWER	Carolyn Yancey
REVIEW DIVISION PM	Kathleen Davies
SEALD REVIEWER	Elektra J. Papadopoulos EJP 8/6/08
SEALD DIRECTOR	Laurie Burke Laurie Burke 8-6-08
REVIEW COMPLETION DATE	August 6, 2008
ESTABLISHED NAME	Certolizumab Pegol
TRADE NAME	Cimzia
APPLICANT	UCB, Inc.
ENDPOINT(S) CONCEPT(S)	Tiredness (fatigue)
MATERIALS REVIEWED	• IND 9869 (SN 732) November 30, 2007 • BLA 125271 (portions related to the claimed concept)
INSTRUMENT(S)	Fatigue Assessment Scale (FAS) SF-36 Vitality domain
INDICATION	Treatment of Rheumatoid Arthritis
INTENDED POPULATION	Adults with active rheumatoid arthritis

A. EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) regarding BLA 125271 for Certolizumab for the treatment of adults with active rheumatoid arthritis (RA). (b) (4)

Fatigue is defined in the scientific literature as the "subjective sensation of generalized tiredness or exhaustion" (Belza, 1990). The burden of fatigue in patients with active RA is high and good measurement of fatigue is important in this patient population. (b) (4)

- Fatigue is a multidimensional concept with physical, cognitive and emotional components. However, it is unclear whether a single-item, as was used in the FAS, can adequately represent the concept. It has not been shown that patients in the target patient population understand the concept similarly and whether the instrument captures the concept completely and appropriately.
- The research study cited by the PRO dossier (Belza, 1990) was a pilot study (N=20) to examine the symptom of fatigue in RA. (b) (4)
- Recall period for FAS and SF-36: For the FAS, patients may have difficulty responding based on the entire week's experiences and may instead be responding based on their most recent or current experience, or even their beliefs (Broderick et al, 2008). Patients probably cannot really average their experience over the entire week as the item seems to ask, and this raises concerns over the accuracy, or validity, of the measure. Similar concerns arise regarding the use of the Vitality Domain of the SF-36, where a 4-week recall period was used.
- Although the SF-36 has been widely used and translated into many languages, we do not have evidence to support use of the FAS in each of these multinational settings. It is unclear what process was used to translate and adapt the scale for populations enrolled and whether the measure has comparable properties between versions. It may be helpful to review an analysis of responses by country to help in interpretation of the study results.
- Although, there were statistically significant differences between treatment groups on the FAS, with replication in independent studies and supportive data were obtained from the Vitality Domain of the SF-36, the magnitude of the treatment effect (active-placebo) in the FAS was modest (1.5 to 1.7 on an 11-point scale). An analysis of proportion of patients meeting an *a priori* responder definition was not specified. It may be helpful to review an analysis of the relative distribution of responses by treatment group to help our interpretation of the study results. This would also provide an indication of the relative proportions of patients who stayed the same and worsened.

- [redacted] (b) (4)

B. STUDY ENDPOINT REVIEW

Cimzia is a TNF inhibitor that was studied in three randomized, placebo-controlled, double-blind studies in adults with active RA with ≥ 9 swollen and tender joints. In two studies, it was administered with MTX and in the third study, Cimzia was administered alone. The primary clinical efficacy endpoints for all three studies were based on signs and symptoms as measured by ACR 20 criteria. The sponsor has also sought claims of radiographic response, physical function response and other patient reported outcomes.

SEALD was consulted for the following PRO endpoints [redacted] (b) (4)

- Tiredness: Fatigue Assessment Scale (FAS) and the SF-36 Vitality Domain
- Productivity: Work Productivity Survey (WPS)

A separate SEALD consult response dated July 10, 2008 was issued regarding the work productivity endpoint.

1 INSTRUMENTS

The Fatigue Assessment Scale is found in Appendix A.
The SF-36 questionnaire is found in Appendix B.

The SF-36 was assessed at baseline and weeks 12, 24, 28, 32, 36, 40, 44, 48, and 52/Withdrawal visit. The user manual for the SF-36 was included in the BLA submission.

The FAS was assessed at baseline, weeks 1, 2, 4, 5, 6, 8, 9, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52/Withdrawal visit.

[redacted] (b) (4)

(b) (4)

3 ENDPOINT MODEL

The co-primary endpoints are:
1. ACR20 response rate at Week 24.
2. Change from baseline in mTSS at Week 52.

Major Secondary Efficacy Endpoints:
- Change from Baseline in mTSS at Week 24.
- Change from Baseline in HAQ-DI at Weeks 24 and 52.
- ACR20 responder rate at Week 52.
- ACR50 and ACR70 responder rates at Weeks 24 and 52.

Other Secondary Endpoints:
A number of other secondary endpoints were listed including physicians' assessments, patients' assessments and imaging assessments.

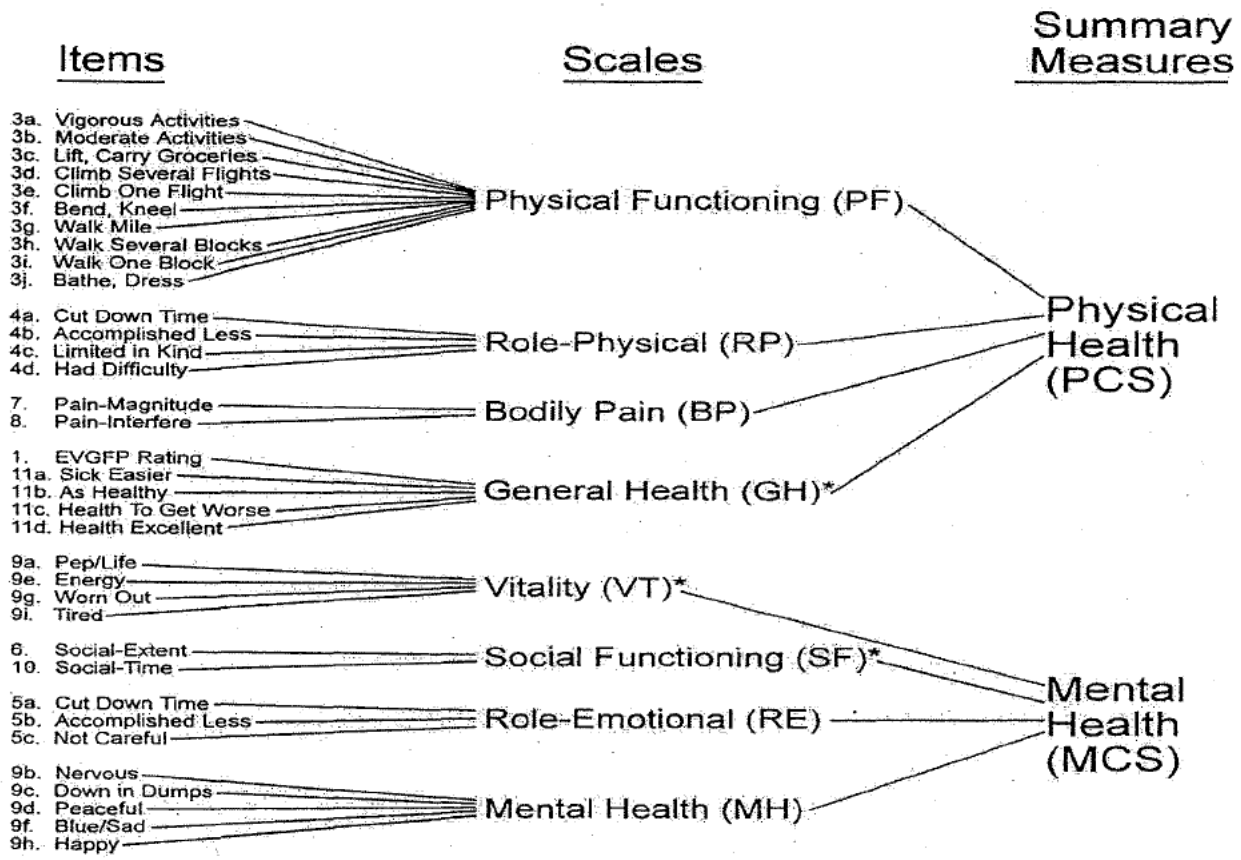
Health Economic and Patient Reported Outcome Endpoints:

Major Secondary PRO Endpoint:
Change from baseline in SF-36 summary scores for physical and mental components, at Weeks 24 and 52.

Other Endpoints
- The SF-36 Health Survey (bodily pain, role physical, physical functioning, role emotional, mental health, social functioning, vitality and general health) subscores at Weeks 12, 24, 36, 48 and 52, and the summary scores at Weeks 12, 36 and 48.
- The Work Productivity Survey.
- The EQ-5D Health State Evaluation (Europe only).
- The HCRU Questionnaire.
- Fatigue Assessment.

Reviewer's comment: The patient reported endpoints were labeled "other endpoints" and did not appear as secondary endpoints in the clinical protocol or analytic plan.

4 CONCEPTUAL FRAMEWORK OF THE SF-36



There are three levels as shown above: (1) items; (2) eight scales; and (3) two summary measures, the MCS and PCS. Each item is used in scoring only one scale. A linear T-score transformation method is used so that both PCS and MCS have a mean of 50 and a standard deviation of 10 in the general U.S. population. Higher scores indication better health status.

This transformation is *not* used in the 0-100 scoring used for the eight domains.

5 CONTENT VALIDITY

SF-36:

The SF-36 (Ware, 1992) is a generic measure of overall health status for use in the general population that produces two summary scores, the mental health component summary score (MCS) and the physical health component summary (PCS). The SF-36 Vitality domain was used as a measure of tiredness in addition to the FAS. The Vitality domain includes four questions that asks patients to rate their level of tiredness ("tired", "worn out") and energy ("full of pep", "energy") on a six-point scale.

The SF-36 items evaluate eight health care concepts. A score per health concept is calculated as follows:

Physical Functioning 3a+3b+3c+3d+3e+3f+3g+3h+3i+3j

Role Physical 4a+4b+4c+4d

Bodily pain 7+8
General health 1+11a+11b+11c+11d
Vitality 9a+9e+9g+9i
Social Functioning 6+10
Role Emotional 5a+5b+5c
Mental health 9b+9c+9d+9f+9h

There is also an unscaled single item (Q2) asking respondents about health change over the past year. SF-36 sub-scales are scored so that a higher score indicates a better health state.

When calculating the SF-36 sub-scores, the items were first to be recoded according to the author's recommendation, then sub-scores were to be computed by summing across items in the same sub-scale (raw sub-scores), and finally the raw sub-scores were to be transformed on a 0-100 scale (transformed sub-scores).

Sub-score = 100 x (Actual raw score – Lowest possible raw score) / (Possible raw score range)

The SF-36 version 1 was used in the clinical trials. This version includes a 4-week recall period.

Fatigue Assessment Scale:
The FAS is a single-item scale in which patients are asked the following: "Please rate your fatigue (weariness, tiredness) during the past week on a scale from 0-10". The sponsor's PRO dossier states the question stem and anchors ("no fatigue" and "fatigue as bad as you can imagine") were almost identical to those reported by Belza (Belza, 1990).

Reviewer's comment: The research by Belza was a pilot study (N=20) to examine the symptom of fatigue in RA, particularly (1) to determine the frequency with which fatigue is a problem and (2) to identify the relationship between fatigue, pain, depression and mood in individuals with RA. This study does not constitute evidence of validity of the PRO instrument in RA as a measure of fatigue or tiredness (b) (4)
The publication also does not provide a representation of the actual instrument that was handed to patients.

6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

SF-36:
The internal consistency reliability of the Vitality domain of the SF-36 was measured by cronbach's alpha coefficient in a population of patients with chronic medical and psychiatric conditions in the US (alpha= 0.87) (McHorney, 1994).

Test-retest reliability (reproducibility) of the SF-36 was assessed in a general practice population in UK. The correlation between the retest scores and the scores of the first administration from

ranged from 0.60 to 0.81, p-value was not specified (Brazier, 1992). The interval between two administrations was 2 weeks.

Fatigue Assessment Scale:
The measurement properties of the FAS including test-retest reliability were not described in the BLA submission.

7 INTERPRETATION OF SCORES

(b) (4)

8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

Study CDP870-027 was conducted in 147 centers in the following countries: Argentina (12), Chile (4), Mexico (3), Estonia (3), Finland (3), Latvia (3), Lithuania (6), Russia (10), Ukraine (10), Bulgaria (6), Croatia (1), Czech Republic (8), Hungary (7), Serbia (5), Slovakia (4), Australia (7), Belgium (4), Canada (13), France (2), Israel (7), New Zealand (5), and the United States (24).

Although the SF-36 has been widely used and translated into many languages, we do not have evidence to support use of the FAS in each of these multinational settings. It is unclear what process was used to translate and adapt the FAS for populations enrolled and whether the measure has comparable properties between versions. This is important in light of the fact that only 7% of the study patients were from the U.S. and the majority of patients (> 60%) were from Eastern Europe and Russian, Baltic States.

9 PROTOCOL AND ANALYSIS PLAN

Study Synopsis CDP870-027:
This was a phase 3 multicenter, double blind, placebo-controlled, parallel group 52-week study to assess the efficacy and safety of 2 dose regimens of lyophilized CDP870 given subcutaneously as additional medication to methotrexate in the treatment of signs and symptoms and preventing structural damage in patients with active RA who have an incomplete response to methotrexate.

There were 147 centers in 22 countries. Coprimary efficacy measures were the ACR-20 response at Week 24 and the mTSS at Week 52. Health Outcome Measures (Health-Related Quality of Life [HRQoL], tiredness [fatigue], productivity) in patients with active RA were secondary objectives in this study. Patients who failed to achieve an American College of Rheumatology (ACR) 20 response at Week 12 (confirmed at the Week 14 visit) were designated as treatment failures and withdrawn.

In this study, discontinuation due to lack of efficacy at week 16 occurred in 63% of patients in the placebo + MTX group, in 21% of patients in the low dose Cimzia + MTX group and in 17% of patients in the high dose Cimzia + MTX group. Missing data were imputed by carrying forward the last efficacy measurements for the FAS, the SF-36 and the WPS.

Reviewer's comment: The PRO assessments for the FAS were scheduled to be collected at Week 16. The SF-36 was collected at week 12, but was not scheduled to be collected at week 16.

Reviewer's comment: The PROs were not secondary endpoints, but rather were included as "other endpoints" in the phase 3 clinical studies. It is important that a testable hypothesis be pre-specified and that a responder definition be prespecified to help in interpreting the study results.

Study Synopsis CDP870-050:
Study CDP870-050 was similar in design to Study CDP870-027, but was 24 weeks in duration and was a much smaller study. There were 76 centers in 13 countries. A total of 619 subjects were randomized (127 to placebo, 246 to CZP 200 mg, and 246 to CZP 400 mg; all with MTX) and all were included in the ITT Population for analysis of efficacy.

Study Synopsis CDP870-011:
This was a phase 3 study of the safety and efficacy of CDP870 400 mg subcutaneously versus placebo in the treatment of the signs and symptoms of patients with RA who have previously failed at least one disease modifying anti-rheumatic drug (DMARD). The study was conducted at a total of 36 Study Centers in 3 countries (Austria, Czech Republic, and the U.S.).

The primary objective was to compare the efficacy of CDP870 400 mg every 4 weeks to placebo in treating the signs and symptoms of patients with RA who have previously failed at least one Disease Modifying Anti-Rheumatic Drug (DMARD). The study of the effect of CDP870 on health- outcomes measures was a secondary objective. The duration of treatment was 24 weeks.

Tiredness as measured by the FAS:
Tiredness was measured with the FAS, an 11-point scale of tiredness and weariness (0-10) and a decrease in FAS indicates reduction in tiredness. The FAS scores at baseline were comparable across the treatment groups in both the phase 3 studies which included every two weeks dosing (CDP870-027 and CDP870-050). The decrease from baseline in the FAS scores was significantly greater ($p<0.001$) in both active groups (CZP 200 mg and 400 mg with background MTX) compared to the control group (placebo plus MTX) at Week 24 (CDP870-027 and CDP870-050) and Week 52 (Study CDP870-027).

Table 1Change from Baseline in Fatigue Assessment Scale at Weeks 24 and 52 in Every 2 Weeks Dosing Studies

	Study CDP870-027			Study CDP870-050		
	PBO + MTX (N=199)	CZP 200 mg + MTX (N=393)	CZP 400 mg + MTX (N=390)	PBO + MTX (N=127)	CZP 200 mg + MTX (N=246)	CZP 400 mg + MTX (N=246)
Baseline						
n	196	391	387	126	244	246
Mean (SD)	6.7 (1.9)	6.4 (2.0)	6.5 (1.9)	6.5 (1.8)	6.7 (1.9)	6.4 (1.8)
Change at Week 24						
Mean change (SD)	-1.0 (2.6)	-2.3 (2.5)	-2.4 (2.4)	-0.5 (2.0)	-2.1 (2.1)	-2.1 (2.3)
Difference vs. PBO + MTX [a][b] (95% CI)		-1.5 (-1.9, -1.2)	-1.6 (-2.0, -1.2)		-1.5 (-1.9, -1.1)	-1.7 (-2.1, -1.3)
P-value		<0.001	<0.001		<0.001	<0.001
Change at Week 52						
Mean change (SD)	-0.9 (2.5)	-2.5 (2.7)	-2.5 (2.6)	NA	NA	NA
Difference vs. PBO + MTX [a] (95% CI)		-1.7 (-2.1, -1.3)	-1.7 (-2.1, -1.3)	NA	NA	NA
P-value		<0.001	<0.001	NA	NA	NA

LOCF imputation method was used for missing data.
[a] Difference in adjusted mean (CZP + MTX minus PBO + MTX) was derived from an ANCOVA with geographic region and treatment as factors, and Baseline score as a

Table 2 Change from Baseline in Fatigue Assessment Scale at Week 24 in Every 4 Weeks Monotherapy Study

	Study CDP870-011			
	PBO (N=109)		CZP 400 mg (N=111)	
	n		n	
Baseline				
Mean (SD)	109	6.2 (2.3)	110	6.4 (2.2)
Change from Baseline at Week 24				
Mean change (SD)	109	0.1 (2.1)	110	-1.4 (3.0)
Difference vs. PBO [a] (95% CI)				-1.4 (2.0, -0.8)
P-value				<0.001

LOCF imputation method was used for missing data.
[a] Difference in adjusted mean (CZP 400 mg minus PBO) was derived from an ANCOVA with country and treatment as factors, and Baseline score as a covariate.

Reviewer's comment: The magnitude of the treatment effect (active-placebo) was modest (1.5 to 1.7 on an 11-point scale). An analysis of proportion of patients meeting an a priori responder definition was not provided.

The proportion of patients achieving an increase of at least 5 points in the SF-36 domains in the every two weeks dosing studies is shown in the following table.

Table 3 Proportion of Subjects with an Increase of at least 5 Points in SF-36 Domains (General Health and Vitality) from Sponsor's Table 7:60 ISE

	Study CDP870-027						Study CDP870-050					
	PBO + MTX		CZP 200 mg + MTX		CZP 400 mg + MTX		PBO + MTX		CZP 200 mg + MTX		CZP 400 mg + MTX	
	N	%	N	%	N	%	N	%	N	%	N	%
General Health												
Week 24												
Response rate [a] (95% CI)	194	13.4 (8.6, 18.2)	370	47.8 (42.7, 52.9)	379	53.6 (48.5, 58.6)	125	9.6 (4.4, 14.8)	244	44.3 (38.0, 50.5)	244	48.0 (41.7, 54.2)
P-value [b]				<0.001		<0.001				<0.001		<0.001
Week 52												
Response rate [a] (95% CI)	194	12.4 (7.7, 17.0)	370	44.9 (39.8, 49.9)	379	45.1 (40.1, 50.1)	NA	NA	NA	NA	NA	NA
P-value [b]				<0.001		<0.001	NA	NA	NA	NA	NA	NA
Vitality												
Week 24												
Response rate [a] (95% CI)	196	13.3 (8.5, 18.0)	375	49.1 (44.0, 54.1)	383	52.0 (47.0, 57.0)	126	8.7 (3.8, 13.7)	246	49.2 (42.9, 55.4)	243	54.7 (48.5, 61.0)
P-value [b]				<0.001		<0.001				<0.001		<0.001
Week 52												
Response rate [a] (95% CI)	196	11.7 (7.2, 16.2)	375	46.7 (41.6, 51.7)	383	47.8 (42.8, 52.8)	NA	NA	NA	NA	NA	NA
P-value [b]				<0.001		<0.001	NA	NA	NA	NA	NA	NA

At week 24, the proportion of patients in study CDP870-027 achieving a 5-point increase in score on the SF-36 Vitality Domain was higher in the active arms, 49.1 and 52.0 (low dose and high dose, respectively), compared with the placebo group, 13.3. This difference was statistically significant. Similarly, study CDP870-050 also showed treatment effect that was statistically significant. The proportions of patients with a 5-point increase in the SF-36 General Health Domain was comparable to what was observed for the Vitality Domain.

The proportion of patients achieving an increase of at least 5 points in the SF-36 domains in the every four weeks dosing study is shown in the following table.

Table 4 Proportion of Subjects with an Increase of at least 5 Points in SF-36 Domains from Sponsor's Table 7:61 ISE

	Study CDP870-014			
	PBO + MTX		CZP 400 mg + MTX	
	n	Mean (SD)	n	Mean (SD)
Physical Functioning				
Baseline mean (SD)	119	37.8 (22.9)	124	36.5 (22.2)
Mean change (SD)	119	2.5 (21.4)	121	13.9 (21.5)
Difference vs. PBO+MTX (95% CI) [a]				10.9 (5.7, 16.2)
P-value				<0.001
Role Physical				
Baseline mean (SD)	117	16.5 (27.7)	125	15.8 (27.4)
Mean change (SD)	117	9.5 (34.6)	122	32.6 (40.9)
Difference vs. PBO+MTX (95% CI) [a]				22.8 (13.9, 31.7)
P-value				<0.001
Bodily Pain				
Baseline mean (SD)	119	27.0 (15.4)	126	28.3 (16.7)
Mean change (SD)	119	10.9 (20.0)	123	22.6 (21.1)
Difference vs. PBO+MTX (95% CI) [a]				12.3 (7.4, 17.2)
P-value				<0.001
General Health				
Baseline mean (SD)	118	39.4 (17.7)	123	35.9 (17.2)
Mean change (SD)	118	3.6 (13.0)	120	11.2 (16.1)
Difference vs. PBO+MTX (95% CI) [a]				6.9 (3.2, 10.5)
P-value				<0.001
Vitality				
Baseline mean (SD)	115	38.5 (16.1)	125	33.9 (18.6)
Mean change (SD)	115	3.80 (17.4)	122	14.7 (19.3)
Difference vs. PBO+MTX (95% CI) [a]				9.3 (4.8, 13.7)
P-value				<0.001
Social Functioning				
Baseline mean (SD)	119	57.9 (27.7)	125	55.7 (25.3)
Mean change (SD)	119	4.4 (26.3)	122	14.1 (24.3)
Difference vs. PBO+MTX (95% CI) [a]				8.9 (3.2, 14.6)
P-value				≤0.01
Role Emotional				
Baseline mean (SD)	116	52.0 (44.2)	123	52.6 (45.0)
Mean change (SD)	116	4.0 (47.4)	120	17.8 (44.5)
Difference vs. PBO+MTX (95% CI) [a]				14.4 (5.0, 23.7)
P-value				≤0.01
Mental Health				
Baseline mean (SD)	115	61.3 (18.5)	123	59.3 (20.6)
Mean change (SD)	115	3.3 (15.1)	120	9.6 (17.2)
Difference vs. PBO+MTX (95% CI) [a]				5.5 (1.7, 9.3)
P-value				≤0.01

Treatment effect was also noted Study CDP870-014, where the difference from placebo was 9.3 in the SF-36 Vitality Domain.

Reviewer's comment: Interestingly, the baseline Mental Health Domain of the SF-36 showed a mean score of approximately 10 points above the average for the general population.

Table 5 Change from Baseline in SF-36 Vitality Domain Score in Study C87027 (LOCF) Adapted from Sponsor's table 11:18 (CSR)

Domains	Placebo + MTX (N = 199)	CZP 200 mg + MTX (N = 393)	CZP 400 mg + MTX (N = 390)
Vitality			
Baseline			
n	196	375	383
Mean (SD)	32.9 (17.4)	35.8 (18.0)	36.1 (18.6)
Change from Baseline at Week 24			
n	174	345	348
Adjusted Mean (SE) [a]	4.7 (1.5)	15.5 (1.1)	16.2 (1.1)
95% CI of Adjusted Mean [a]	[1.8, 7.5]	[13.4, 17.6]	[14.1, 18.2]
Difference [b] vs. PBO + MTX[a]			
Adjusted Mean [95% CI]		10.9 [7.4, 14.3]	11.5 [8.1, 15.0]
P-value		p<0.001	p<0.001
Change from Baseline at Week 52			
n	174	350	350
Adjusted Mean (SE) [a]	4.5 (1.5)	15.1 (1.0)	15.6 (1.0)
95% CI of Adjusted Mean [a]	[1.6, 7.3]	[13.1, 17.2]	[13.6, 17.7]
Difference [b] vs. PBO + MTX [a]			
Adjusted Mean [95% CI]		10.7 [7.2, 14.1]	11.2 [7.8, 14.6]

(a) ANCOVA with region and treatment as factors and Baseline as covariate

In Study C87027, the mean baseline score was somewhat lower in the placebo arm (32.9) compared with the Cimzia groups (35.8 and 36.1). A higher reduction in tiredness from baseline in the SF-36 Vitality Domain was observed in the active treatment arms compared with placebo. At week 24, the absolute difference was 10.9 and 11.5 points on a scale from 0 to 100 for Cimzia (200 mg)-Placebo and Cimzia (400 mg)-Placebo, respectively.

Reviewer's comment: The change from baseline in the other domains of the SF-36 (e.g., General Health) also showed evidence of treatment effect in this study (data not shown).

The following table summarizes the change from baseline in mean SF-36 Vitality Domain using LOCF.

Table 6 Change from Baseline in SF-36 Vitality Domain Score in Study C87050 (LOCF) Adapted from Sponsor's table 11:17 (CSR)

Domain	Placebo + MTX (N = 127)	CZP 200 mg + MTX (N = 246)	CZP 400 mg + MTX (N = 246)
Vitality			
Baseline			
N	126	246	243
Mean (SD)	36.90 (18.67)	36.00 (17.66)	38.14 (17.19)
Change from Baseline at Week 24			
N	116	230	228
Adjusted Mean (SE) [(a)]	2.05 (1.56)	11.80 (1.16)	13.27 (1.18)
95% CI of Adjusted Mean [(a)]	[-1.01, 5.11]	[9.53, 14.08]	[10.94, 15.59]
Difference [(b)] vs PBO + MTX [(a)] Adjusted Mean [95% CI]		9.75 [6.21, 13.30] [(c)]	11.22 [7.67, 14.77] [(c)]

(a) ANCOVA with region and treatment as factors and Baseline as covariate
(c) $p<0.001$

In Study C87050, a higher reduction in tiredness from baseline in the SF-36 Vitality Domain was observed in the active treatment arms compared with placebo. The absolute difference was 9 and 11 points on a scale from 0 to 100 for Cimzia (200 mg)-Placebo and Cimzia (400 mg)-Placebo, respectively. The mean of the VT domain scores at baseline ranged from 36-38 points with SD of 17-18 points across the three treatment groups.

Reviewer's comment: For both Studies C87050 and C87027, the baseline scores indicated impairment in this patient population with respect to the SF-36 Vitality domain, because the average for the general population is 50 on a scale from 0-100.

10 REFERENCES

Belza Tack, B Self-reported Fatigue in Rheumatoid Arthritis: A Pilot Study. Arthritis Care and Research. 1990;3(3) 154-157

Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, Westlake L. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ. 1992 Jul 18;305(6846):160-4

Broderick, JE et al The accuracy of pain and fatigue items across different reporting periods. Pain 2008 (in press) doi:10.1016/j.pain.2008.03.024.

McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF 36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994 Jan;32(1):40-66

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473-83

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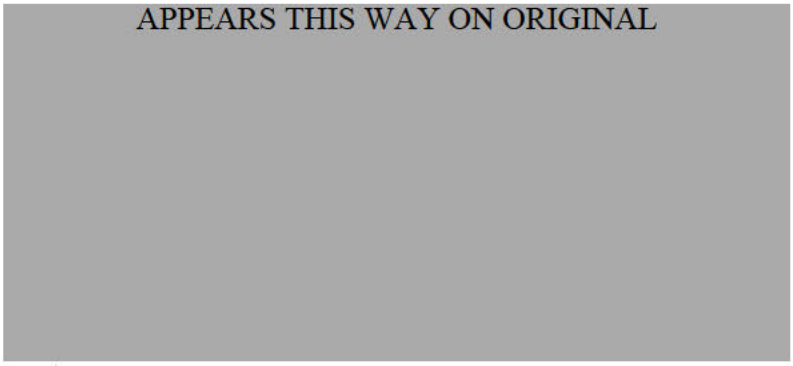

APPENDIX A

FATIGUE ASSESSMENT

The patient will answer the following question: < QUFATI >

"Please rate your fatigue (weariness, tiredness) **during the past week**, on a scale of 0-10."

No Fatigue	0	1	2	3	4	5	6	7	8	9	10	**Fatigue as bad as you can imagine**

[DSPN]

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

CHEMISTRY REVIEW(S)

Product Quality Review Data Sheet

1. **BLA#** STN 125271/0

2. **REVIEW #:** 1

3. **REVIEW DATE:** 15-Jul-08

4. **REVIEWERS:** Gurpreet Gill-Sangha, Ph.D
Barbara Rellahan, M.S., Ph.D. Reviewer and Team Leader

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS:**

Communication/Document	Date
pre-BLA meeting	27-Jun-2008
Filing Review memo (45 days).	25-Jan-2008
(b) (4)	15-Feb-2008
Information Request Letter	14-Mar-2008
Information Request Letter	09-May-2008
Information Request Letter	02-Jul-2008
Teleconference	15-Jul-2008

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
STN 125271/0 Original Submission	29-Nov-2007
STN 125271/0/1	15-Feb-2008
STN 125271/0/2	14-Mar-2008
STN 125271/0/4	16-May-2008
STN 125271/ (submitted by email)	28-Jul-2008
STN 125271/ (submitted by email)	31-Jul-2008

7. **NAME & ADDRESS OF APPLICANT:**

Name: UCB Pharma, Inc.
Address: 1960 Lake Park Drive
Smyrna, GA 30080
USA
Representative: (b) (6)
Telephone: 770-970-8592

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: Cimzia
b) Non-Proprietary/USAN: Certolizumab Pegol
c) Code name: CDP870(CAS) registry number is 428863-50-7
d) Common name: CDP870 Fab'-PEG
e) Drug Review Status: Lyophilized product for Crohn's Disease approved April 22, 2008
f) Chemical Type: PEGylated recombinant immunoglobulin Fab' fragment

9. **PHARMACOL. CATEGORY:** Therapeutic PEGylated recombinant immunoglobulin Fab' fragment to human tumor necrosis factor alpha.

10. **DOSAGE FORM:** Sterile parenteral solution.

11. **STRENGTH/POTENCY:**
    a) The concentration of Cimzia Drug Product is 200 mg/ml.
    b) Potency is defined as percent IC_{50} value relative to the reference standard, (b) (4)
    c) Dating period for pre-filled syringe drug product is 18 months when stored at 2°C -8°C and protected from light.
    d) Certolizumab pegol is filled into 1 mL glass syringes containing 200 mg of Cimzia.

12. **ROUTE OF ADMINISTRATION:** Subcutaneous injection.

13. **ACID (Animal Component Information Database)**
Refer to BLA 125160 review for animal/human derived component information. Also see section 3.2.S.2.3.1 Control of Source and Starting Materials of Biological Origin.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies, NIH Bldg 29B, HFD-123
29B Lincoln Drive, Bethesda, MD 20892

The Quality Team Leader's Executive Summary

From:	Barbara Rellahan, M.S., Ph.D. Division of Monoclonal Antibodies (DMA)
Through:	Patrick Swann, Ph.D., Deputy Director, DMA Kathleen Clouse, Ph.D., Director, DMA
BLA Number:	125271/0
Product:	Cimzia™ (Certolizumab Pegol, CDP870)
Sponsor:	UCB Inc.
Date of Review:	August 11, 2008

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of Cimzia leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets the parameters recommended by FDA. The manufacturing process results in a consistent product as evidenced by results from different production runs including the validation campaign.

The following should be communicated to sponsor in the approval letter:

The dating period for Cimzia pre-filled syringe drug product shall be 18 months from the date of manufacture when stored at 2–8°C. The date of manufacture shall be defined as the date of (b) (4) of the formulated drug product. The dating period for bulk drug substance shall be (b) (4) We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of drug product and drug substance under 21 CFR 601.12.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The CMC review team has communicated comments and questions to the sponsor throughout the review period in an attempt to resolve concerns. Our most recent communication with the sponsor was on 15-Jul-08. Replies to this inquiry were received on 28-Jul-08. Two issues remain unresolved and will need to be addressed as CMC Post-Marketing Commitments. These issues are outline below.

1. Provide a commitment to re-evaluate the drug product sub-visible particulates release and shelf-life specifications upon confirming the feasibility of a preparatory method that will enable implementation of the USP <788> preferred method.
2. Provide a commitment to conduct additional studies to evaluate the process-specific assay test for the assessment of HCP per your 31-Jul-08 submission. A summary report and data will be provided by 15 December 2008.

II. Summary of Chemistry Assessments

A. Drug Product and Drug Substance

- CIMZIA (certolizumab pegol; CDP870) is supplied as a sterile, liquid injection, in a graduated 1 ml, glass Pre-Filled Syringe (PFS) for subcutaneous administration. The pH is approximately 4.7. Each single-use PFS contains approximately 200 mg certolizumab pegol, 1.36 mg sodium acetate, and 7.31 sodium chloride. No preservatives are present.

- The drug product is supplied as 200 mg liquid certolizumab pegol in a sterile, single-use (b) (4) syringe with a staked needle in a 1 ml long Type 1 glass (USP<661>) syringe barrel. The needle, which is staked to the glass barrel, is fitted with a needle shield that includes a rubber and plastic component ((b) (4) that will be inserted in the (b) (4) syringe barrel to seal the container closure system after filling.

- (b) (4) .

- The drug product is filled using (b) (4) (b) (4)

- Stability of the drug product has been established for 18 months at 2-8°C for commercial scale product and for (b) (4) These results currently support an 18-month expiry. The drug product stability protocol in the BLA is acceptable.

- Certolizumab pegol is a recombinant, humanized Fab' antibody fragment directed against TNF-α, (b) (4) to PEG2MAL40K, (b) (4) . The experimentally determined molecular mass of the Fab' fragment is approximately (b) (4) The experimentally determined molecular mass of certolizumab pegol is approximately 90.8 kDa, (b) (4)

- The Fab' fragment is manufactured in *Escherichia coli*. The Drug Substance is produced during specific manufacturing campaigns carried out at (b) (4) (b) (4)

- (b) (4).

(b) (4)

- The proposed expiration dating period for storage of Drug Substance based on the data is (b) (4). The Drug Substance stability protocol and commitment in the BLA is appropriate.

- Raw material testing and control is adequate. (b) (4). Based on information available to date, (b) (4) has been deemed to pose a minimal risk for (b) (4).

- (b) (4)

(b) (4)

[redacted]

- CDP870 binds to TNF-α with a binding constant of 89.0 ± 4.9 pM. Potency of the Drug Product is determined by (b) (4) [redacted]

B. Description of How the Drug Product is Intended to be Used

Cimzia has been approved for use in the treatment of Crohn's disease (BLA 125160) and is also intended for use for the treatment of Rheumatoid Arthritis.

Cimzia is supplied as a sterile, 1ml liquid in pre-filled syringe format; the resulting pH is approximately 4.7. The syringe is fitted with a staked 25G x 1/2" thin wall needle and closed using a (b) (4) [redacted] Each syringe is presented pre-assembled with a plunger rod and pad, extended

finger flange and barrel sleeve, and a (b) (4) overcap. Each syringe is intended for single use. Syringes should be stored at 2-8°C and should not be frozen. Cimzia should be at room temperature at the time of administration of injection. The words "200 mg/ml" written on the side of the syringe label will turn green when the product is ready to be injected. The full contents of each syringe are injected subcutaneously into separate sites on the abdomen or thigh.

Each Cimzia commercial pack contains 1 single dose tray containing 2 prefilled syringes, 2 alcohol swabs, and an information leaflet. The proposed recommended adult dose for Cimzia is an induction regimen of 400 mg given as two subcutaneous injections at weeks 0, 2, and 4, followed by a maintenance regimen of 400 mg every 4 weeks. Refer to the clinical review for further information on the dosing regimen for induction and maintenance.

Cimzia vials should be refrigerated at 2-8°C. The recommended expiration dating period is 18 months under these storage conditions. The expiry could be extended as additional stability data is provided.

Cimzia approved for the treatment of Crohn's Disease is supplied as a sterile, white, lyophilized powder for reconstitution with 1 mL sterile Water for Injection (WFI), USP; the resulting pH is approximately 5.2. The commercial Crohn's Disease Cimzia pack contents include two 5 mL lyophilized Type I glass vial with rubber stopper overseals each containing 200 mg lyophilized Cimzia for reconstitution, two 2 mL Type I glass vials containing 1 mL sterile WFI, two 3 mL plastic syringes, four 20 gauge luer-lok needles (1 inch), two 23 gauge luer-lok needles (1 inch) and eight alcohol swabs.

The proposed recommended adult dose for Cimzia's lyophilized format for Crohn's Disease is an induction regimen of 400 mg given as two subcutaneous injections at weeks 0, 2, and 4, followed by a maintenance regimen of 400 mg every 4 weeks. Refer to the clinical review for further information on the dosing regimen for induction and maintenance.

Both the lyophilized powder and liquid in PFS Cimzia formats are proposed to be marketed simultaneously. The drug substance for both formats is manufactured by a (b) (4) . After reconstitution of the lyophilized formulation with 1 mL of sterile Water for Injection, USP, the resulting pH is approximately 5.2. Each single-use vial contains approximately 200 mg certolizumab pegol, 100 mg sucrose, 0.9 mg lactic acid, and 0.1 mg polysorbate. The liquid in PFS format contains 200 mg/mL certolizumab pegol in 10 mM sodium acetate and 125 mM sodium chloride, pH 4.7. *In vitro* analytical tests have not revealed significant differences between the lyophilized and PFS formats. However, demonstration of full comparability would require additional *in vivo* studies (e.g., to determine the impact of different excipients on bioavailability).

During review of the manufacturing process for the Cimzia PFS format, several revisions were made to the drug substance and drug product release and stability specifications

(addition of two new release criteria and narrowing of several other release criteria) which provide a higher degree of control over drug product quality, but have not resulted in alteration to any critical quality attribute of the drug product. (b) (4)

There are some stability differences in the drug product formats over the course of the drug product shelf-life, (b) (4) which are more likely to be observed in the liquid format compared to the lyophilized format.

C. Basis for Approvability or Not-Approval Recommendation

- Cimzia is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. Cimzia is manufactured consistently, resulting in a safe and effective product.

Quality unit Assessment

I. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

The review of module 3.2 is attached as a separate document.

II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

UCB claims categorical exclusion from the requirements of environmental assessment (BLA section 1.3.1.5) based on:

- 21CFR25.31(b) - "Action on an application for marketing approval of a biologic product for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substances, its metabolites, or degradation products in the environment".

UCB concludes that CDP870 is a humanized antibody Fab fragment-polyethylene glycol (PEG) conjugate composed of naturally occurring amino acids. In addition, UCB states that PEGs are reported to be practically non-toxic, with no adverse effects observed in rats at levels of 2% in the diet (approximately equivalent to 100 mg/kg bw/day) (reference BLA section 4.3.195 for toxicological review of PEG and PEGylated polypeptides). The maximum amount of PEG2MAL expected to be used in the manufacture of CDP870 drug substance per year is (b) (4)

III. LIST OF DEFICIENCIES TO BE COMMUNICATED

The following postmarketing commitments are needed to confirm that the manufacturing process is validated and to assure adequate product quality. The following needs to be communicated to the sponsor.

Please amend the BLA with your written agreement to conduct the following postmarketing commitments:

1. To re-evaluate the drug product sub-visible release and shelf-life specifications upon confirming the feasibility of a preparatory method that will enable implementation of the USP <788> preferred method. Data and specification assessment will be provided within 2 years from the time of approval.
2. Provide a commitment to conduct additional studies to evaluate the process-specific assay test for the assessment of HCP per your 31-Jul-08 submission. A summary report and data will be provided by 15 December 2008.

Administrative

A. Reviewers' Signature

Product Reviewer: Gurpreet Gill-Sangha, Ph.D. (left the agency in June 2008)

Product Team Leader/Reviewer: Barbara Rellahan, M.S., Ph.D. Barbara Rellahan 8/12/08

B. Endorsement Block

Product Deputy Division Director: Patrick Swann, Ph.D. 8/12/08

Product Division Director: Kathleen Clouse, Ph.D. Kathleen Clouse 08/12/08

C. CC Block

OBP Office Director: Steve Kozlowski, M.D.
DAARP CDTL Jeffery Siegel, M.D.
Division of Monoclonal Antibodies File/BLA STN 125160

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

PHARMACOLOGY REVIEW(S)

FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

SUPERVISORY MEMO TO FILE

BLA#:	**125,271**
Drug Substance:	Cimzia® (Certolizumab pegol)
Serial Submission/Date:	No formal submission; August 29, 2008 (e-mail response)
Sponsor:	**UCB Inc.**
Division name:	Division of Anesthesia, Analgesia, and Rheumatology Products
HFD #:	170
Date of Memo:	9/24/2008

Recommendation: The Applicant's explanation is acceptable to address concerns previously raised in the BLA review regarding the potential presence of the (b) (4) in the Drug Substance/Product and as a product of metabolic degradation. No further information is requested nor is any action necessary.

Background: As described in the primary review of Dr. Gary Bond and my Supervisory Memo, the concern was raised that the drug product utilized a (b) (4) . In particular, genetic toxicity and reproductive toxicity (teratogenicity) have been demonstrated. The review team was unable to find other approved biologic drugs which have used a similar (b) (4) and, although the drug was recently approved by the Division of Gastroenterology Products for Crohn's Disease it was noted there were no specifications for (b) (4) or the modified (b) (4) An additional concern which was raised was the potential for release of the (b) (4) in vivo with breakdown of the drug product. The Applicant was asked to address these two issues (presence of (b) (4) and related species in drug substance/product; in vivo fate) in a Request for Information sent on 8/21/2008.

The Applicant provided a response in an e-mail of August 29, 2008. According to this response, there is no (b) (4) at any point during drug synthesis. The Fab' fragment of CDP870 (the "drug substance" of Cimzia®) is (b) (4) which could be present are (b) (4)

[redacted] but have been evaluated and quantified through historical batch analysis. The Applicant also maintains that should any [redacted] be added to the drug synthesis process it would very likely react with the [redacted] to give a [redacted] If [redacted] escaped this [redacted] step it would be removed during the [redacted]

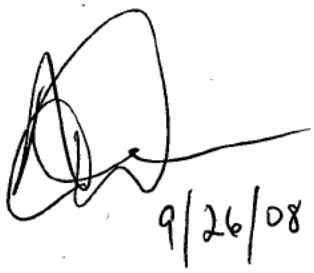
The Applicant addressed the in vivo fate of the CDP870 [redacted] by stating that the reaction of the [redacted] of the Fab' fragment results in a stable [redacted]. [redacted] as described in the package therefore ceases to exist as an entity. The Applicant agrees there are no studies which have examined the metabolic fate of this type [redacted] but notes that excretion studies in the BLA have observed that the two [redacted] PEG chains are excreted as a [redacted] form. However, they do not know if the [redacted] is only via a [redacted] or whether the [redacted] portion of the [redacted] are also present. There is no [redacted] which could regenerate the [redacted]. Support for the safety of [redacted] was provided by a table comparing the acute toxicity of simple [redacted] inhalation effects, skin effects, eye effects, sensitization, genetic toxicology and reproductive toxicology obtained from Sigma Aldrich MSDS. Although simple [redacted] appears less toxic than the [redacted] no information on [redacted] was available, however, on the latter two species.

The Applicant's response was provided to the Office of Biotechnology Products' Division of Monoclonal Antibodies Dr. Barbara Rellahan who consulted with Serge Beaucage of the Division of Therapeutic Proteins. Dr. Beaucage considers the Applicant's explanation accurate and plausible and felt there was no chance of exposure to [redacted] from product or product degradation. He noted that the potential by-product of the [redacted] process described by the Applicant are [redacted] however, but are controlled in the [redacted] production process and due to their reactivity would be unlikely to be un-reacted and in the event they did exist would be removed by the steps outlined by the Applicant.

Recommendations:
The Applicant's explanation is acceptable to address concerns previously raised in the BLA review. No further information is requested nor is any action necessary.

External Comments:
None.

Adam Wasserman, Ph.D.
Supervisory Pharmacologist, DAARP



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Supervisory Pharmacologist Memorandum

BLA NUMBER:	**125,271**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**0/0/2008**
PRODUCT:	
Trade Name:	**Cimzia®**
Established Name:	**Certolizumab pegol**
INDICATION:	**Rheumatoid arthritis**
INTENDED CLINICAL POPULATION:	**Adults with active rheumatoid arthritis**
SPONSOR:	**UCB, Inc.**
DOCUMENTS REVIEWED:	**Primary review of Dr. Gary P. Bond; Primary review of Dr. Sushanta Chakder (DGP); electronic submission as necessary.**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)**
PHARM/TOX REVIEWER:	**Gary P. Bond, Ph.D., DABT**
PHARM/TOX SUPERVISOR:	**Adam Wasserman, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Kathleen Davies**

EXECUTIVE SUMMARY

I. BACKGROUND

Cimzia (certolizumab pegol) is a recombinant fusion protein consisting of the Fab' portion of an humanized anti-TNFα antibody specific for human TNFα which is further conjugated to polyethylene glycol (PEG) to provide more desirable pharmacokinetic characteristics. Cimzia was approved in April 2008 for use in Crohn's Disease (CD) by the Division of Gastroenterology Products. Cimzia represents the fourth TNFα blocker allowed for use on the U.S. market with others being infliximab (Remicade®; Centocor, BLA 103,772 approved 1998), etanercept (Enbrel®; BLA 103,795 approved 1998) and adalimumab (Humira®; Abbot, BLA 125,057 approved 2002). Infliximab, etanercept, and adalimumab are approved for use in adults with rheumatoid arthritis (RA), the indication for which the Applicant is currently seeking for Cimzia in this Supplement. As noted by Dr. Bond in his primary review, the current dosing strategy proposed for the RA indication is identical to the approved CD regimen when monthly maintenance dosing is utilized (400 mg SC every 4 weeks). The clinical comparability, safety, and efficacy of the proposed alternative maintenance dosing strategy (200 mg SC every 2 weeks) are the subject of review by other disciplines.

A. Regulatory Summary (Pharmacology/Toxicology)

Cimzia was submitted for the CD indication to the Division of Gastroenterology Products in February 2006 and was not approved at that time pending a complete response to deficiencies. All nonclinical studies supporting the submission were reviewed by the DGP reviewer, Dr. Sushanta Chakder, who recommended BLA approval without additional nonclinical evaluation. Cited deficiencies were addressed in a 2nd cycle resubmission which was ultimately approved in April 2008. The only substantive difference between the CD and RA submissions in regards to a nonclinical evaluation would be the difference in formulation. The approved Cimzia product for CD utilizes a lyophilized powder reconstituted for injection whereas the drug formulation for the RA submission is a "Ready to Use" Injectible formulation format. A pre-BLA meeting held with the Applicant on June 27, 2007 contained the following nonclinical advice:

> "... an assessment of the composition of the new formulation relative to the formulation evaluated for BLA 125169 regarding impurities, degradants and inactive ingredients will be required. Should differences in non-product-related impurities or excipients elicit a safety concern, further evaluation, including toxicologic qualification, may be necessary."

No new nonclinical studies were provided in this supplement which required review by Dr. Bond.

II. MAJOR NONCLINICAL ISSUES IDENTIFIED IN PRIMARY REVIEW

As identified in the primary review of Dr. Bond, the Fab' fragment specific for human TNFα is linked to two 40 KDa PEG molecules by a (b) (4) (b) (4) . At present there is no information available which indicates this (b) (4) has been used in any FDA-approved biologic products though it is clear this (b) (4) is being examined for drug development and is being given in clinical studies. The manufacture of the drug substance and control of impurities in the drug substance and product is reviewed as part of the Product Review for the Crohn's Disease BLA application (125,169) originally completed by Gupreet Gill-Sangha, Ph.D. which was subsequently modified for the RA supplement by Barbara Rellahan, Ph.D. The Applicant has provided specifications for the PEG (b) (4) product which would include the (b) (4) Additionally, the stability of the drug substance in vivo upon administration and the possible release of the (b) (4) has not been evaluated or addressed in the application. As noted by Dr. Bond, this compound is associated with significant toxicity due to its reactive nature. (b) (4) has been shown to be genotoxic in vitro and is a teratogenic reproductive toxicant when evaluated in isolation. Mechanistic studies implicate direct intercalation into DNA as well as direct inhibition of the catalytic sites of topoisomerase II. There is no information on (b) (4) concern would seem warranted given sufficient exposure.

III. RECOMMENDATIONS

A. Recommendation on approvability

The primary nonclinical reviewer, Dr. Gary Bond, recommends approval of the supplement and I concur with this recommendation.

B. Recommendation for nonclinical studies

No nonclinical studies are recommended for approval of the supplement. Further information is being requested of the Applicant at this time, specifically any available data on levels of (b) (4) in the drug substance and product as well as information on the stability of the drug product in vivo and potential release of (b) (4). Should this information not be available, I concur with Dr. Bond that the Applicant should evaluate these levels and, if found, develop specifications for (b) (4). The recommendation of Dr. Bond for data on human exposure levels to (b) (4) may be ultimately appropriate; however, an in vitro assay providing data on stability of the drug substance in human blood or other proper matrix may be sufficient to allow the Applicant to address this issue and should be included as part of an overall risk evaluation with

human use. Should the Applicant be unable to provide information on the levels [redacted] (b) (4) the following post-marketing commitments will be sought:

1. Provide an evaluation of the levels of [redacted] (b) (4) in the drug substance and drug product. If this compound is found, provide specifications and rationale based on an evaluation of human risk.

2. Provide an evaluation of the potential for in vivo release [redacted] (b) (4) Evaluation of stability in serum or other appropriate matrix should be provided unless otherwise justified.

C. Recommendations on labeling

I concur with the modification proposed by Dr. Bond on the approved Cimzia® label.

8/25/08

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

BLA NUMBER:	**125,271**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**December 6, 2007**
PRODUCT:	**Cimzia® (Certolizumab Pegol)**
INTENDED CLINICAL POPULATION:	**Rheumatoid Arthritis**
APPLICANT:	**UCB, Inc.**
DOCUMENTS REVIEWED:	**eCTD**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia and Rheumatology Products**
PHARM/TOX REVIEWER:	**Gary P. Bond, Ph.D., DABT**
PHARM/TOX SUPERVISOR:	**Adam M. Wasserman, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Kathleen Davies, M.S.**
DATE OF REVIEW SUBMISSION:	**August 21, 2008**

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EXECUTIVE SUMMARY

I. Background & Regulatory Issues

Cimzia® (certolizumab pegol) is a recombinant, humanized, antibody Fab' fragment with high specificity for human TNFα. It is conjugated to two, linked (b) (4) polyethylene glycol (PEG) chains *via* a (b) (4) molecule. Cimzia® is proposed for the treatment of Rheumatoid Arthritis by subcutaneous injection using a single use, pre-filled syringe. Cimzia was approved for treatment of Crohn's disease by the Division of Gastroenterology Products (BLA 125,160) on April 22, 2008 in the form of a reconstituted lyophilized powder for the same applicant UCB Inc. Approved dosing with Cimzia® for Crohn's Disease is 400 mg subcutaneously at weeks 0, 2 and 4 and, if response occurs, followed with 400 mg subcutaneously every four weeks. Comparable dosing is proposed for Rheumatoid Arthritis at 400 mg subcutaneously at weeks 0, 2, and 4 followed by 200 mg every other week with alternative doses of 400 mg every four weeks can be considered as a maintenance dose. Support for the different dosing regimen from the approved dose has been addressed by clinical biopharmacology studies and/or clinical trials.

II. Recommendations

A. Recommendation on approvability

BLA supplement approval is recommended.

B. Recommendation for nonclinical studies

None recommended for the active pharmaceutical ingredient for this supplement to BLA 125,160, which also had no recommendation for nonclinical studies. While no additional nonclinical studies are required for supplement approval, as a Post-Marketing action, the Applicant will be asked to address the potential presence of the (b) (4), which is acutely toxic, genotoxic, and a reproductive toxin. The Applicant will be asked to determine (b) (4) levels in the drug substance and drug product. If present at significant levels, the sponsor may need to determine levels in humans, conduct a risk assessment, and set appropriate specification levels, all subject to Agency review. Based on these results, further action may be required to ensure human safety.

C. Recommendations on labeling

Proposed Pharm/Tox-based label sections of July 21, 2008 match approved PLR-format label of BLA 125,160 for Cimzia®. The only change, with 125,160 reviewer approval, was to correctly refer to rodent-specific TNFα molecule as cTN3. (b) (4), in Section 13.1 as was correctly done in section 8.1. See entire Pham/Tox-based labeling sections 8.1 (Pregnancy) and 13.1 (Carcinogenesis, Mutagenesis, and Impairment of Fertility) at the end of the full review.

III. Summary of nonclinical findings

A. Brief overview of nonclinical findings (summarized from BLA 125,160 review of Dr. Sushanta Chakder)

Toxicology studies with Cimzia® were conducted in monkeys involving administration of single and multiple doses of the clinical product. Intravenous administration of single doses up to 870 mg/kg was well-tolerated without any treatment-related adverse effects. In repeat dose studies, Cimzia was administered weekly. In a 28-day i.v. toxicity study in monkeys, decreased hemoglobin, RBC, and packed cell volume was observed immediately after administration of 50, 100 & 400 mg/kg weekly doses. Increased WBC levels were observed in male and female monkeys receiving 10 & 100 mg/kg subcutaneous doses for 13 & 26 weeks. Hematological parameters returned to their normal levels following a 13-week treatment-free recovery period. Histiocytic vacuolation in the hemolymphoreticular tissues (splenic red pulp, medullary sinuses of the mandibular and mesenteric lymph nodes, bone marrow, thymus) were observed in animals treated with the 400 mg/kg dose for 28 days. Vacuolation (foamy macrophages) was also observed in different organs (choroid plexus, adrenals, mesenteric and mandibular lymph nodes, lamina propria of the urinary bladder, spleen and endometrial stromal mucosa of the uterus) in monkeys receiving a 100 mg/kg weekly subcutaneous doses for 13, 26 or 52 weeks. While vacuolation of macrophages within the hemolymphoreticular tissues may be related to the pharmacological effects of the drug, this observation was present at reduced severity after the recovery period. An increase in the activated partial thromboplastin time (APTT) was observed in monkeys receiving 50 & 100 mg/kg doses for 52 weeks. A similar increase in the APTT was also observed in an *ex vivo* study with monkey blood. However, no effects on APTT were observed in animals receiving the drug for 13 or 26 weeks.

The genotoxic potential for Cimzia® was assessed in the bacterial reverse mutation assay (Ames assay), the human peripheral blood lymphocyte chromosomal aberration assay and the mouse bone marrow micronucleus assay. Cimzia® was not genotoxic in any of these assays.

Cimzia® binds to human TNFα (HTNF) with high affinity and cross-reacts with TNFα from non-human primates. However, Cimzia® does not recognize TNFα from rodents. So, instead of using Cimzia®, the sponsor used the pegylated Fab fragment (cTN3 PF) to a homologous rat anti-TNF antibody (cTN3γ1) to conduct Segment I (fertility and early embryonic development), Segment II (teratogenicity), and Segment III (pre- and post-natal development) studies. In the Segment I fertility and early embryonic development study in rats, male and female animals were treated with 0, 20 & 100 mg/kg i.v. doses of cTN3 PF, administered twice weekly. cTN3 PF had no effects on the fertility and early embryonic development in rats. In the segment II teratogenicity study with cTN3

PF in rats, the test agent was administered intravenously at 0, 20 & 100 mg/kg doses on gestation days 1 and 4, or gestation days 6, 9, 13, & 16. cTN3 PF was not teratogenic in rats at the doses examined. cTN3 PF had no adverse effects on the pre- and post-natal development of rats at i.v. doses up to 100 mg/kg (bi-weekly).

B. Pharmacologic activity (modified from BLA 125,160)

There is considerable evidence that excessive tumor necrosis factor alpha (TNFα) activity is involved in the pathogenesis of inflammatory disease, most notably rheumatoid arthritis (RA). Cimzia® (certolizumab pegol) is a recombinant, humanized antibody Fab' fragment with specificity for human TNFα. Cimzia® binds to recombinant human TNFα with high affinity (K_d, about 90 pM). It also binds to cynomolgus monkey TNFα with a much lower affinity (about 1/40th of that of human TNFα), but does not bind to rat, mouse, guinea pig and rabbit TNFα.

The binding affinity of Cimzia® for human TNFα is higher than that of infliximab and adalimumab and lower than that of etanercept. It neutralizes soluble and membrane TNFα, inhibits binding of TNFα to human TNF receptors, and inhibits LPS-induced cytokine production in human monocytes. In addition, Cimzia® neutralizes the biological activity of human TNFα *in vivo* in animals in which TNFα was the physiologically active molecule. It inhibits human TNFα-induced neutrophil accumulation in the peritoneal cavity of mice, pyrexia in rabbits, and chronic inflammatory polyarthritis in transgenic mice. Cimzia® does not mediate antibody-dependent cell-mediated cytotoxicity or complement-mediated cell toxicity; it is therefore not cytotoxic to TNF-expressing cells.

PEGylation of HTNF IgG with the 40 KD (kilodalton) PEG increased the elimination half-life ($t_{1/2\alpha}$) of the compound in monkeys following a single i.v. dose. The plasma exposure level for the 40 KD PEGylated Fab' (Cimzia®) was higher than that for the (b) (4) PEGylated Fab' (78% and 30% of the non-PEGylated Fab', respectively). PEGylation also decreased the immunogenicity of the antibody. In rats also, Cimzia® also had longer half-life and higher plasma exposure levels than that of the Fab' fragment alone following an i.v. dose. Following subcutaneous administration of a single dose (3 or 31 mg/kg) to monkeys, plasma concentrations of Cimzia® increased with increasing dose, and the maximum plasma concentrations were reached between 24 and 48 hours with a $t_{1/2}$ of about 200 hours (8.4 days). The estimated bioavailability in rats following s.c. administration was 23.5% in males and 33.8% in females. Tissue distribution of Cimzia® in rats following an i.v. dose was similar to that of the non-PEGylated form. At 3 hours following administration, the highest level was found in the kidneys, followed by lung, liver and spleen. Cimzia® was not an inhibitor of P-glycoprotein. In humans, following subcutaneous (up to 800 mg) or intravenous (up to 10 mg) administration, the C_{max} and AUC values increased with increasing dose, and the peak Cimzia® concentrations were attained between 54 and 171

hours following s.c. administration. The terminal elimination half-life ($t_{1/2}$) was approximately 14 days for all doses tested. Following s.c. administration to humans for 12 weeks, anti-Cimzia® antibodies were detected in 5% (at 800 mg/4 week dose) to 67% (at 50 mg/4 week dose) of the subjects, depending on the doses administered. The presence of the antibody decreased Cmax and AUC by more than 50%.

C. Nonclinical safety issues relevant to clinical use

There are no changes in this review from the original, approved nonclinical review for the active pharmaceutical ingredient (API) from BLA 125,160 and no nonclinical safety issues with the API for rheumatoid arthritis patients. Proposed doses are equivalent to those in approved BLA 125,160 for patients with Crohn's disease and Crohn's patients and are considered by the medical review team to be clinically comparable to rheumatoid arthritis patients making the nonclinical safety assessments conducted for BLA 125,160 relevant to BLA 125,271. In addition, clinical trials support proposed doses for patients with rheumatoid arthritis. However, as the drug substance and drug product contains (b) (4) molecule for the PEG and protein, it may be present as an impurity, degradant, and/or metabolite with the possibility for human exposure.

(b) (4), is a synthetic chemical for which drug substance and drug product levels have apparently not been evaluated or reported and no specification levels proposed. (b) (4) (b) (4) (b) (4) For example, even though dosing will only be every 4 weeks, which will have to be considered in any risk assessment, at a 400 mg dose of Cimzia®, a level of (b) (4) would result in a (b) (4) dose at the maximum allowable daily level for this class of genotoxic agents of (b) (4) The sponsor will be asked to address potential safety issues as a post-marketing action.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

BLA number: 125,271 (supplement to BLA 125,160)
Review number: 1
Sequence number/date/type of submission: 000/November 29, 2007/original
Information to sponsor: Yes ( ) No (x)
Applicant and/or agent: UCB Inc., 1950 Lake Park Drive, Smyrna, GA 30080
Manufacturer for drug substance:

CDP870 Drug Substance Manufacturing and Testing Sites

Reviewer name: Gary P. Bond, Ph.D., DABT
Division name: Division of Anesthesia, Analgesia and Rheumatology Products

Drug:

Trade name: Cimzia®
Generic name: Certolizumab pegol
Code name: CDP870, PHA738144
Chemical name: gHTNF40Fab' 40 kDa PEG. Certolizumab pegol is a

recombinant humanized antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNFα)

CAS registry number: NA

Molecular formula/molecular weight: 90,000 Daltons

(b) (4)

[redacted]

Relevant INDs/NDAs/DMFs:

IND 11, 197, Certolizumab pegol, for treatment of Crohn's disease; UCB Inc., Smyrna, GA

BLA 125,160, Certolizumab pegol, for treatment of Crohn's disease; UCB Inc., Smyrna, GA (approved April 22, 2008)

IND 9,869, Certolizumab pegol, for treatment of rheumatoid arthritis; UCB Inc., Smyrna, GA.

Drug class: Tumor necrosis factor (TNF) blocker

Intended clinical population: Rheumatoid arthritis

Clinical Dose & Dosing for BLA 125,271:

Doses and dosing for proposed BLA 125,271 are considered comparable to those for approved BLA 125,160 and/or are supported by clinical data in rheumatoid arthritis patients.

Dosage and administration:

Approved doses for Cimzia® under approved BLA 125,160:

- 400 mg subcutaneously at Weeks 0, 2 and 4
- If response occurs, follow with 400 mg subcutaneously every four weeks

Proposed doses for Cimzia® under BLA 125,271:

- 400 mg subcutaneously at Weeks 0, 2 and 4 followed by 200 mg every other week
- Alternative doses of 400 mg every four weeks can be considered as a maintenance dose

Clinical formulation:

The drug substance is manufactured at [redacted] (b) (4) The drug product is manufactured at [redacted] (b) (4).

The proposed commercial presentation is a single use, pre-filled syringe fitted with a staked 25G x ½" thin wall needle. Use of the pre-filled syringe is supported by studies which demonstrated the compatibility of the drug formulation with the components of the syringe/closure variants, evaluated extractables and leachables, and confirmed the suitability of the container/closure system. Data from an open label follow-up clinical study has been provided to show that patients can easily self-administer the drug from the pre-filled syringe and are able to safely use the device.

The pre-clinical and Phase I/II clinical programs, supporting both BLA 125,160 for Crohn's Disease (CD) and BLA 125,271 for Rheumatoid Arthritis (RA), commenced with a liquid formulation, initially a 20 mg/mL injection for intravenous administration followed by a 200 mg/mL injection for subcutaneous administration. Each vial contained 200 mg Cimzia® Drug Substance in [redacted] (b) (4) Due to the increase in product-related impurities, notably acidic species observed in stability studies on both Cimzia® Drug Substance and Cimzia® Drug Product, the development of alternative formulations continued. The lyophilized formulation (200 mg/mL Cimzia® Drug Substance, 100 mg/mL sucrose, 0.1 mg/mL Polysorbate 20, and 0.9 mg/mL lactate at pH 5.2 on reconstitution) was introduced at Phase III for Rheumatoid Arthritis and Crohn's Disease and was the product approved for the CD indication. To provide a more patient convenient presentation of Cimzia®, and to simplify the manufacturing process, a new liquid formulation was developed. The resulting formulation, 200 mg/mL Cimzia®, [redacted] (b) (4) at pH 4.7, was introduced into the clinic at Phase III for both RA and CD, and is the proposed commercial formulation for the RA indication.

A complete analytical package has been provided as evidence of equivalence between these two formulations. Additionally, the clinical results generated from studies of lyophilized and liquid formulations provide evidence of clinical equivalence between the two formulations. UCB, Inc. has also conducted a bioavailability study to further support the comparability between the lyophilized and liquid formulations.

The PEG:protein [redacted], which has no specification levels proposed, is a potential impurity, degradant, and metabolite-related human safety concern. It has been reported to be acutely toxic (ip, iv, and oral dosing), genotoxic (Ames and Mouse Lymphoma assays), and have reproductive toxicity (embryo-fetal abnormalities and post-implantation mortality) as referenced in the Micromedex Database Registry of Toxic Effects of Chemical Substances and Toxnet – August 11, 2008 (individual studies not reviewed). [redacted]. According to both the electrophilic properties and the spatial requirements of the substituents, the effects were found to be up to [redacted] times stronger than those of [redacted] and up to [redacted] times stronger than those of [redacted] respectively. The distinct electron-acceptor behavior of the [redacted] compounds allow this [redacted]. As part of a post-marketing action, the sponsor will be asked to address this issue by determining drug substance and drug product levels of [redacted] If significant levels are determined to be present, human blood levels may need to be determined and a human health risk assessment conducted. As a result, specification levels will need to be set for [redacted] or the molecule may need to be replaced with another [redacted] For example, even though dosing will only be every 4 weeks, which will have to be considered in any risk assessment, at a 400 mg dose of Cimzia®, a level of [redacted] would result in a [redacted] dose at the maximum allowable daily level for this class of genotoxic agents of [redacted]. The sponsor will be asked to address potential safety issues as a post-marketing action.

Route of administration: subcutaneous

Disclaimer: Any tabular and graphical information are constructed by the applicant or reviewer of BLA 125,160 unless cited otherwise. Text may be taken directly or modified from the applicant's submission or the review of BLA 125,160.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of BLA 125,271 are owned by UCB, Inc. or are data for which UCB, Inc. has obtained a written right of reference. Any information or data necessary for approval of BLA 125,271 that UCB, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2)

a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that UCB, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of BLA 125,271.

Studies reviewed within this submission: none (all submitted studies have been reviewed for BLA 125,160)

Studies not reviewed within this submission: all submitted studies (studies have been reviewed for BLA 125,160)

2.6.2 PHARMACOLOGY (reviewed and summarized as part of BLA 125,160)

2.6.2.1 Brief summary - NA

2.6.2.2 Primary pharmacodynamics - NA

2.6.2.3 Secondary pharmacodynamics - NA

2.6.2.4 Safety pharmacology - NA

2.6.2.5 Pharmacodynamic drug interactions - NA

2.6.3 PHARMACOLOGY TABULATED SUMMARY – NA

2.6.4 PHARMACOKINETICS/TOXICOKINETICS (reviewed and summarized as part of BLA 125,160)

2.6.4.1 Brief summary - NA

2.6.4.2 Methods of Analysis - NA

2.6.4.3 Absorption - NA

2.6.4.4 Distribution - NA

2.6.4.5 Metabolism - NA

2.6.4.6 Excretion - NA

2.6.4.7 Pharmacokinetic drug interactions - NA

2.6.4.8 Other Pharmacokinetic Studies - NA

2.6.4.9 Discussion and Conclusions - NA

2.6.4.10 Tables and figures to include comparative TK summary - NA

2.6.5 PHARMACOKINETICS TABULATED SUMMARY - NA

2.6.6 TOXICOLOGY (reviewed and summarized as part of BLA 125,160)

2.6.6.1 Overall toxicology summary - NA

2.6.6.2 Single-dose toxicity - NA

2.6.6.3 Repeat-dose toxicity - NA

2.6.6.4 Genetic toxicology - NA

2.6.6.5 Carcinogenicity - NA

2.6.6.6 Reproductive and developmental toxicology - NA

2.6.6.9 Discussion and Conclusions - NA

2.6.6.10 Tables and Figures - NA

2.6.7 TOXICOLOGY TABULATED SUMMARY - NA

OVERALL CONCLUSIONS AND RECOMMENDATIONS (modified from BLA 125,160)

Conclusions:

CDP870 is a humanized antibody Fab' fragment with specificity for human TNFα, which is manufactured in *E. coli* and then conjugated to two, linked (b) (4) polyethylene glycol (PEG) chains. CDP870 binds to human TNFα with high affinity *in vitro*, and neutralizes the biological activity of TNFα *in vitro* and *iv vivo*. The sponsor submitted BLA 125,160 for use of Cimzia® for the treatment of Crohn's disease, which was approved in April 2008, and this BLA for the treatment of rheumatoid arthritis.

Cimzia® binds to human TNFα with high affinity and weakly cross-reacts with TNFα from non-human primates. However, Cimzia® does not recognize TNFα from rodents. So, toxicity studies with Cimzia® were conducted in cynomolgus monkeys. In repeat dose toxicity studies in monkeys, slight hematological changes (decreased hemoglobin, RBC and packed cell volume, increased WBC) were observed and these changes were reversible. In addition, vacuolation of several tissues, particularly hemolymphoreticular tissues were observed in animals receiving high doses. This may be related to the pharmacological actions of the drug. About 5% of the animals receiving i.v. or subcutaneous doses of Cimzia® developed anti-Cimzia antibodies. Cimzia® was not

genotoxic in a battery of genotoxicity assays. As CDP870 does not cross-react with TNFα from rodents, reproductive toxicity studies (Segment I fertility and early embryonic development, Segment II teratogenicity and Segment III pre- and post- natal development) were conducted in rats using a pegylated Fab fragment (cTN3 PF) to a homologous rat anti-TNF antibody (cTN3 γ1). cTN3 PF had no effects on the fertility and early embryonic development; it was not teratogenic and had no effects on pre- and post- natal development in rats. Thus, the preclinical studies with Cimzia® suggest that the sponsor's proposed dose of the product appears to be safe for the treatment of patients with rheumatoid arthritis.

Determination of potential human exposure and a risk assessment for (b) (4) , will be recommended as a Post-Marketing action because (b) (4) has been reported to be acutely toxic (ip, iv, and oral dosing), genotoxic (Ames and Mouse Lymphoma assays), and have reproductive toxicity (embryo-fetal abnormalities and post-implantation mortality).

Unresolved toxicology issues: As a Post-Marketing action, the sponsor will be asked to determine the presence of the (b) (4) with appropriate response thereafter (e.g., none required, risk assessment, specification level, elimination).

Recommendations: The sponsor conducted adequate preclinical studies with Cimzia® to determine the safety of the biological drug and the sponsor's proposed dose appears to be safe for the proposed indication. At this point, from a nonclinical standpoint, the BLA supplement application is recommended for approval. As a Post-Marketing action, the sponsor is recommended to determine (b) (4) levels in the drug substance and drug product. If present at significant levels, the sponsor may need to determine levels in humans, conduct a risk assessment, and set appropriate specification levels. Based on these results, further action may be required to ensure human safety. All of this information should be submitted to the Agency for review.

Suggested labeling: matches approved labeling for reference biological BLA 125,160

- sponsor's most current proposed labeling (April 22, 2008) and approved labeling for BLA 125,160 (listed below) (b) (4) All other changes/additions in label include rheumatoid arthritis-specific wording, which do not impact on Pharmacology/Toxicology label sections.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B – Because certolizumab pegol does not cross-react with mouse or rat TNFα, reproduction studies were performed in rats using a rodent anti-murine TNFα pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol. Reproduction studies have been performed in rats at doses up to 100 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to cTN3 PF. There are, however, no adequate and well-controlled studies of CIMZIA in pregnant women.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies of CIMZIA have not been conducted to assess its carcinogenic potential. Certolizumab pegol was not genotoxic in the Ames test, the human peripheral blood lymphocytes chromosomal aberration assay, or the mouse bone marrow micronucleus assay.

Since certolizumab pegol does not cross-react with mouse or rat TNFα, reproduction studies were performed in rats using a rodent anti-murine TNFα pegylated Fab fragment (b) (4) cTN3 PF), similar to certolizumab pegol. (b) (4) cTN3 PF had no effects on the fertility and general reproductive performance of male and female rats at intravenous doses up 100 mg/kg, administered twice weekly.

Signatures (optional):

Reviewer Signature Gary P. Bond August 21, 2018
Gary P. Bond, Ph.D., DABT date

Supervisor Signature 8/21/18
Adam M. Wasserman, Ph.D. date

Concurrence Yes X No ___

APPENDIX/ATTACHMENTS - none

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125271 / 00
Drug Name:	Cimzia ® (certolizumab pegol)
Indication(s):	Treatment of adults with active rheumatoid arthritis
Applicant:	UCB, Inc.
Date(s):	Letter date: 12/6/07
	PDUFA date: 10/5/08
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Kate Meaker, M.S.
Concurring Reviewers:	Dionne Price, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Clinical Team:	Medical Officer: Carolyn Yancey, M.D.
	Medical Team Leader: Jeffrey Siegel, M.D.
Project Manager:	Kathleen Davies

Keywords: Clinical studies; BLA review

1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

The goal of this application is to evaluate the efficacy and safety of Cimzia for the treatment of adults with active rheumatoid arthritis (RA). Cimzia was approved for treatment of Crohn's disease in April 22, 2008.

The applicant's recommended dosing regimen for treatment of RA is 200 mg every 2 weeks (q2w) after a loading dose of 400 mg on Weeks 0, 2 and 4. This dosing regimen was included in two of the prospectively planned clinical studies. The primary efficacy endpoint was the American College of Rheumatology (ACR) 20 responder endpoint. In both studies, Cimzia 200 mg in combination with methotrexate (MTX) was statistically superior to placebo in combination with MTX for the percent of patients who achieved the ACR20 criterion.

The applicant also included evidence of efficacy based on the 400 mg dose, administered either every 2 weeks or every 4 weeks, in a total of four clinical studies. The primary efficacy endpoint was the same for those studies. Those dosing regimens also were statistically superior to placebo in all the comparisons.

Based on these results, there is sufficient evidence to support the 200 mg q2w dosing regimen (following 3x400 mg q2w loading dose) for Cimzia for initiation of the treatment of RA, and for the 400 mg q4w dosing regimen for maintenance.

1.2 Brief Overview of Clinical Studies

The applicant presented results from four prospectively planned clinical studies to support the RA indication. All four were randomized, double-blind, placebo-controlled, parallel arm, multicenter studies. Two of the studies (50 and 27) were considered by the applicant as primary because those included treatment arms at the recommended dosing regimen of 200 mg every 2 weeks with the 3x400 mg q2w loading dose. Those studies also included treatment arms receiving 400 mg q2w with no loading dose. In studies 11 and 14, dosing was every 4 weeks (q4w). Table 1 presents a comparison of the study dosing details.

At a pre-BLA meeting on June 27, 2007, the applicant discussed these four study designs, clinical endpoints, and analysis plans with DAARP. Part of the discussion considered which dosing regimens (200 mg q2w; 400 mg q2w; 400 mg q4w) would potentially support indication statements. The conclusion was that each dose regimen would be evaluated on safety and efficacy concerns, and the wording of proposed indication statements could not be determined until after full review.

Table 1: Efficacy Studies in Rheumatoid Arthritis Patients

Study Number (Dates Conducted)	Number of Centers (Locations)	Treatment arms			Sample Size	Duration of Treatment
		Treatment	Dosing Regimen	Loading Dose		
CDP870-011 (6/03 – 7/04)	36 (US; Austria; Czech Republic)	Cimzia Placebo (mono-therapy)	400 mg q4w q4w	None	n=111 n=109	24 weeks
CDP870-014 (10/02 – 1/04)	43 (US and Europe)	Cimzia + MTX Placebo + MTX	400 mg q4w q4w	None	n=124 n=119	24 weeks
CDP870-027 (2/05 – 9/06)	147 (22 countries: North and South America, Europe, Australia, New Zealand)	Cimzia + MTX Cimzia + MTX Placebo + MTX	200 mg q2w 400 mg q2w q2w	400 mg Weeks 0, 2, 4 None	n=393 n=390 n=199	52 weeks
CDP870-050 (6/05 – 9/06)	76 (US and Europe)	Cimzia + MTX Cimzia + MTX Placebo + MTX	200 mg q2w 400 mg q2w q2w	400 mg Weeks 0, 2, 4 None	n=246 n=246 n=127	24 weeks

1.3 Statistical Issues and Findings

There were no statistical issues involved with the analyses of these four clinical studies. Two of the studies included two dose regimens for Cimzia and compared each to placebo, with an appropriate adjustment for multiplicity (Bonferroni method). Study 27 had two primary endpoints and used a prespecified hierarchical closed testing approach.

2. Introduction

2.1 Overview

Cimzia (certolizumab) is currently approved for treatment of Crohn's disease in adults. It is a tumor necrosis factor (TNF) blocker and is administered by subcutaneous injection.

The applicant submitted four double-blind, placebo-controlled, parallel arm studies in adult RA patients to support the addition of the indication for the treatment of active RA in adults. My statistical review focuses on two studies, referred to as Studies 27 and 50, because those included treatment arms receiving the proposed dosing regimen of 200 mg q2w after a loading dose of 3x400 mg q2w. Studies 011 and 014 provide supportive information on a different dosing regimen. All four studies included dosing regimens of 400 mg at either q2w or q4w schedules. Table 1 on the previous page provides more details on the dosing regimens tested.

2.2 Data Sources

All data was supplied by the applicant to the CBER electronic data room (edr) in SAS transport format. All necessary documentation, formats, and links were provided as well. The data and final study report for the electronic submission were archived under the network path location \\cbsap58\m\EDR Submissions\2007 BLA\DCC60005785\roadmap.pdf

3. Statistical Evaluation

3.1 Evaluation of Efficacy

Study CDP870-027 (conducted 2/05 to 9/06)

Design

Study 27 was a randomized, double-blind, parallel arm, multi-center study. The goal was to evaluate the safety and efficacy of Cimzia in adult subjects with rheumatoid arthritis. This study had two objectives. The first objective was to evaluate Cimzia for the treatment of signs and

symptoms in RA. For this objective, efficacy was measured at Week 24 using the ACR20 endpoint. The second objective was to investigate Cimzia for the inhibition of progression of structural damage. For this objective, efficacy was measured at Week 52 using x-rays which were assessed using the modified Total Sharp Score (mTSS) scale for structural damage in the joints.

Eligible patients had to have a diagnosis of adult-onset RA of at least 6 months but less than 15 years prior to screening. Active RA was defined using ACR criteria of ≥9 tender joints, ≥9 swollen joints, and elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels. Patients were also on a stable dose of methotrexate (MTX) at screening and continued on the same dose as part of the treatment regimen. There were three treatment arms; Cimzia 200 mg q2w (after a loading dose of 400 mg at Week 0, 2, and 4) + MTX; Cimzia 400 mg q2w + MTX; and placebo + MTX. After screening and baseline assessments, patients were randomized at a 2:2:1 ratio to the three arms.

Patients were randomized and received the first treatment injection at Week 0. Patients returned for injections and assessments every two weeks for up to 52 weeks of treatment. Patients who did not achieve the ACR20 criterion at Week 12, (with confirmation at Week 14) were required in the protocol to withdraw for lack of efficacy at Week 16 and were classified as treatment failures.

There are two primary endpoints for this study: the proportion of ACR20 responders at Week 24 and the change from baseline in mTSS at Week 52. The study was planned to test them in a hierarchical, closed-testing, order to control the overall Type I error rate.

The ACR20 endpoint was defined as ≥20% improvement in the number of tender and swollen joints and ≥20% improvement in 3 of the 5 remaining core set measures: patient's and physician's global assessment of disease activity; patient's assessment of arthritis pain; HAQ-Disability Index (HAQ-DI), and CRP. The primary timepoint was Week 24.

Secondary endpoints at Week 24 included the ACR50 and ACR70 responder endpoints, which are similar to the ACR20 but use 50% and 70% cutoffs, respectively. The seven separate components of the ACR core measures were also secondary endpoints.

At Week 52, the mTSS score was calculated from x-rays taken at baseline and week 52. It was a function of the joint erosion score and joint-space narrowing score.

The protocol planned to compare each of the Cimzia + MTX arms to the placebo + MTX arm for the ACR20 responder endpoint. The Bonferroni adjustment for multiple comparisons was applied, therefore each comparison used two-sided α=0.025.

All primary efficacy comparisons were conducted on the Intent-to-Treat (ITT) population consisting of all randomized patients. Additional sensitivity analyses were conducted on the per protocol population consisting of those patients who had no major protocol deviations.

For the ACR20/50/70 endpoints, all patients who discontinued were classified as non-responders. For the mTSS score, patients who discontinued prior to Week 52 had x-rays at the withdrawal visit. Week 52 values were imputed using linear extrapolation for those patients. This was prespecified in the protocol, and at the pre-BLA meeting (6/2707) DAARP considered this to be reasonable approach. For both primary outcomes, the applicant conducted numerous sensitivity analyses.

Patient Disposition

Patients were adult males and females with rheumatoid arthritis. A total of 982 patients were randomized to the study, 393 to the Cimzia 200 mg q2w treatment group, 390 to the Cimzia 400 mg q2w treatment group, and 199 to the placebo group. Table 2 shows the distribution of patient discontinuations and reasons.

A larger proportion of patients in the placebo group were discontinued at Week 16 due to lack of efficacy. There was a predefined requirement in the protocol that patients who did not achieve the ACR20 criterion by Week 12 were discontinued at Week 16. This difference in discontinuations was not unexpected. The discontinuations were classified as non-responders for the primary efficacy analyses.

Table 2: Patient Disposition (Study 27)

	Cimzia 200 mg q2w + MTX	Cimzia 400 mg q2w + MTX	Placebo + MTX
Randomized	n=393	n=390	n=199
Total Discontinued	138 (35%)	116 (30%)	156 (78%)
Withdrawn for Lack of Efficacy per protocol	83 (21%)	68 (17%)	125 (63%)
Discontinued			
Lack of Efficacy	15 (4%)	6 (2%)	16 (8%)
Adverse Event	17 (4%)	22 (6%)	3 (2%)
Non-compliance	4 (1%)	3 (1%)	0
Withdrew consent	15 (4%)	11 (3%)	10 (5%)
Lost to Follow-up	1 (0%)	1 (0%)	1 (1%)
Other	5 (1%)	6 (2%)	3 (2%)
Completed	255 (65%)	274 (70%)	43 (22%)

Source: Clinical Study Report Table 10.1; Figure 10.1

Baseline Demographics

The three treatment groups were well balanced with respect to relevant demographic and baseline characteristics as shown in Table 3.

Table 3: Patient Demographics (Study 27)

	Cimzia 200 mg q2w + MTX n=393	Cimzia 400 mg q2w + MTX n=390	Placebo + MTX n=199
Age (years)			
Mean (SD)	51 (12)	52 (12)	52 (11)
Range	19-81	21-83	18-78
Age categories:			
<65 yrs	341 (87%)	331 (85%)	173 (87%)
≥65 yrs	52 (13%)	59 (15%)	26 (13%)
Gender			
Female	324 (82%)	326 (84%)	167 (84%)
Male	69 (18%)	64 (16%)	32 (16%)
Race			
Caucasian	363 (92%)	349 (89%)	179 (90%)
Hispanic/Latin Am.	20 (5%)	34 (9%)	16 (8%)
African-American	4 (1%)	2 (1%)	2 (1%)
Other	6 (2%)	5 (1%)	2 (1%)
Weight (kg)			
Mean (SD)	74 (17)	73 (16)	74 (17)
BMI (kg/m^2)			
Mean (SD)	27 (6)	27 (6)	28 (6)
BMI categories:			
<25	154 (39%)	152 (39%)	77 (39%)
25-29	135 (34%)	131 (34%)	66 (33%)
≥30	103 (26%)	104 (27%)	55 (28%)

Region			
Central/South America	60 (15%)	63 (16%)	30 (15%)
Eastern Europe	141 (36%)	136 (35%)	71 (36%)
Russia/Baltic/Scandinavia	123 (31%)	122 (31%)	62 (31%)
Rest of World	69 (18%)	69 (18%)	36 (18%)
U.S.	28 (7%)	25 (6%)	14 (7%)

Sources: Clinical Study Report Tables 11.2 and 11.3

Efficacy Results

For the responder endpoints, ACR 20/50/70, the analyses used a logistic regression model, with terms for treatment and region in the model. Region was used rather than center because there were a large number of centers (147 centers in 22 countries). This was prespecified in the protocol.

In the results for the ACR response variables, the applicant did not include subjects who were missing all ACR assessments. This dropped a few from the denominator per group (5 from Cimzia 200 group; 2 from Cimzia 200 group, and 1 from placebo group) I calculated the results with all missing set to non-responder and the results were consistent.

The change from baseline to Week 52 in mTSS score was analyzed using an analysis of covariance (ANCOVA) model on the rank of change from baseline with treatment and region as factors and rank of baseline value as the covariate. The applicant included a calculation of the percent inhibition for mTSS using the mean change from baseline in mTSS for the Cimzia and placebo groups. This was calculated as % inhibition = (1 – (change from baseline in mTSS in active treatment / change from baseline in mTSS in control treatment)) *100. The DAARP clinicians requested this to assess the inhibition of progression claim.

A total of 74 patients (8%) were dropped from the primary analysis of mTSS because they did not have any x-ray data post-randomization. The numbers dropped per group were 29 from Cimzia 2300 mg, 27 from Cimzia 400, and 18 from placebo. This was a slightly higher percentage in the placebo group (9%) than in the Cimzia groups (7% each). The applicant conducted three sensitivity analyses to impute data for these patients, and all showed similar results.

For the seven components of the ACR, mean changes from baseline were analyzed using an ANCOVA model with treatment and region as factors and baseline value as the covariate. For the HAQ-DI scale, Dr. Yancey requested that I also provide a responder analysis, where a responder was defined as having at least a 0.22 unit decrease in HAQ-DI from baseline to Week 24.

The results of the analyses are presented in Table 4. For the two primary endpoints, all comparisons were statistically significant in favor of each Cimzia treatment arm versus placebo. The secondary endpoints demonstrated a significant effect of Cimzia compared to placebo.

Table 4: Efficacy Results (Study 27)

	Cimzia 200 mg q2w + MTX n=393	Cimzia 400 mg q2w + MTX n=390	Placebo + MTX n=199
Primary Endpoint at Week 24			
ACR 20 (% responders)	228/388 59%	236/388 61%	27/198 14%
Difference vs. placebo	46%	47%	
Odds Ratio vs. placebo	9.2 (5.5, 15.6)	10.1 (5.5, 15.6)	
p-value	<0.001	<0.001	
Secondary Endpoints at Week 24			
ACR 50 (% responders)	144/388 (37%)	155/388 (40%)	15/198 (8%)
ACR 70 (% responders)	83/388 (21%)	80/388 (21%)	6/198 (3%)
ACR components [LS Mean Change from base (Std Error)]:			
Number of tender joints	-18 (0.6)	-19 (0.6)	-4 (0.9)
Number of swollen joints	-14 (0.4)	-14 (0.5)	-3 (0.6)
Patient global – disease activity (VAS)	-30 (1.2)	-32 (1.2)	-8 (1.6)
Physician global – disease activity (VAS)	-37 (1.0)	-37 (1.1)	-12 (1.5)
Patient assessment of arthritis pain (VAS)	-30 (1.1)	-32 (1.1)	-8 (1.6)
HAQ-DI	-0.6 (0.03)	-0.6 (0.03)	-0.2 (0.04)
CRP ratio to baseline (Geometric mean)	0.44	0.40	0.89
HAQ-DI responder (change ≤ -0.22)	216/388 (56%)	231/388 (60%)	30/198 (15%)
Primary Endpoint at Week 52			
Change from baseline mTSS	n=364	n=364	n=181
Mean (SD)	0.4 (6)	0.2 (5)	2.8 (8)
p-value (ANCOVA on ranks)	<0.001	<0.001	
% Inhibition vs. Placebo+MTX	85%	92%	

Sources: Clinical Study Report Tables 11.11, 11.13, 11.14; SAS datasets

Study CDP870-050 (conducted 6/05 to 9/06)

Design

Study 50 was a randomized, double-blind, parallel arm, multi-center study. The objective was to evaluate the safety and efficacy of Cimzia in adult subjects with rheumatoid arthritis. The treatment duration in this study was 24 weeks, so the only primary efficacy assessment was the ACR20 to support the indication for the treatment of signs and symptoms in RA.

Aside from the length of treatment, this study design was similar to Study 27. The eligible patient criterion, three treatment arms, primary and secondary efficacy assessments through week 24, and analyses were the same. X-ray data was collected at baseline and at Week 24. The change from baseline in mTSS was included as a secondary endpoint.

The primary efficacy analysis, as planned in the protocol, was to compare each of the Cimzia + MTX arms to the placebo + MTX arm for the ACR20 responder endpoint. The Bonferroni adjustment for multiple comparisons was applied, therefore each comparison used two-sided α=0.025. All efficacy comparisons used the Intent-to-Treat (ITT) population for the primary analyses. Additional sensitivity analyses looked at the per protocol population. For the ACR20/50/70 endpoints, all patients who discontinued were classified as non-responders.

Patient Disposition

Patients were adult males and females with rheumatoid arthritis. A total of 619 patients were randomized to the study, 246 to the Cimzia 200 mg q2w treatment group, 246 to the Cimzia 400 mg q2w treatment group, and 127 to the placebo group. Table 5 shows the distribution of patient discontinuations and reasons.

As seen in study 27, a larger proportion of patients in the placebo group discontinued at Week 16 due to lack of efficacy. There was a predefined requirement in the protocol that patients who did not achieve the ACR20 criterion by Week 12 were discontinued at Week 16. This difference in discontinuations was not unexpected. Those who discontinued were classified as non-responders for the primary efficacy analyses.

Table 5: Patient Disposition (Study 50)

	Cimzia 200 mg q2w + MTX	Cimzia 400 mg q2w + MTX	Placebo + MTX
Randomized	n=246	n=246	n=127
Total Discontinued	72 (29%)	65 (26%)	110 (87%)
Withdrawn for Lack of Efficacy per protocol	52 (21%)	52 (21%)	103 (81%)
Discontinued			
Lack of Efficacy	2 (1%)	1 (<1%)	4 (3%)
Adverse Event	11 (5%)	6 (2%)	2 (2%)
Non-compliance	1 (<1%)	2 (1%)	1 (1%)
Withdrew consent	5 (2%)	3 (1%)	0
Lost to Follow-up	0	0	0
Other	1 (<1%)	1 (<1%)	0
Completed	174 (71%)	181 (74%)	17 (13%)

Source: Clinical Study Report Figure 10.1; Table 10.1

Baseline Demographics

The two treatment groups were well balanced with respect to relevant demographic and baseline characteristics as shown in Table 6.

Table 6: Patient Demographics (Study 50)

	Cimzia 200 mg q2w + MTX n=246	Cimzia 400 mg q2w + MTX n=246	Placebo + MTX n=127
Age (years)			
Mean (SD)	52 (11)	52 (12)	52 (12)
Range	22-81	19-77	22-78
Age categories:			
<65 yrs	213 (87%)	205 (83%)	112 (88%)
≥65 yrs	33 (13%)	41 (17%)	15 (12%)

Gender			
Female	206 (84%)	192 (78%)	107 (84%)
Male	40 (16%)	54 (22%)	20 (16%)
Race			
Caucasian	239 (97%)	242 (98%)	126 (99%)
Hispanic/Latin Am.	6 (2%)	1 (<1%)	1 (<1%)
African-American	0	1 (<1%)	0
Other	1 (<1%)	2 (1%)	0
Weight (kg)			
Mean (SD)	73 (15)	73 (15)	72 (15)
BMI (kg/m^2)			
Mean (SD)	27 (5)	27 (5)	26 (5)
BMI categories:			
<25	113 (46%)	96 (39%)	54 (43%)
25-29	77 (31%)	95 (39%)	48 (38%)
≥30	56 (23%)	55 (22%)	25 (20%)
Region			
Central/South America	0	0	0
Eastern Europe	118 (48%)	123 (50%)	61 (48%)
Russia/Baltic/Scandinavia	98 (40%)	101 (41%)	53 (42%)
Rest of World	30 (12%)	22 (9%)	13 (10%)
U.S.	21 (9%)	17 (7%)	9 (7%)

Sources: Clinical Study Report Tables 11.2 and 11.3

Efficacy Results

The analysis models were the same as in Study 27. The only difference in the planned analyses was that the change in baseline in mTSS endpoint was measured at Week 24 (rather than Week 52 in study 27). The applicant describes this as a "major secondary" endpoint in this study.

For the ACR response variables, the sponsor did not include one subject in the Cimzia 400 mg group due to all ACR measures being missing. I checked the results with all missing set to non responder and the results remained the same.

For the mTSS analysis, a total of 71 patients (11%) were excluded because they were missing all post-randomization x-ray data. The discontinuation rates were similar across the groups: 32 (13%) in the Cimzia 200 mg group; 24 (10%) in the Cimzia 400 mg group; and 15 (12%) in the

placebo group. The applicant conducted three sensitivity analyses using different imputation strategies. All showed results similar to the main analysis.

The results of the analyses are presented in Table 7. For the primary endpoint, each of the Cimzia treatment arms was statistically significantly superior versus placebo. The secondary endpoints also showed significant difference for Cimzia vs. placebo.

Table 7: Efficacy Results (Study 50)

	Cimzia 200 mg q2w + MTX n=246	Cimzia 400 mg q2w + MTX n=246	Placebo + MTX n=127
Primary Endpoint at Week 24			
ACR 20 (% responders)	141/246 57%	141/245 58%	11/127 9%
Difference vs. placebo	48%	49%	
Odds Ratio vs. placebo	14.4 (6.7, 31.0)	14.3 (6.7, 30.8)	
p-value	<0.001	<0.001	
Secondary Endpoints at Week 24			
ACR 50 (% responders)	80/246 (33%)	81/245 (33%)	4/127 (3%)
ACR 70 (% responders)	39/246 (16%)	26/245 (11%)	1/127 (1%)
ACR components [LS Mean Change from base (std error)]:			
Number of tender joints	-17 (0.8)	-20 (0.8)	-4 (1.0)
Number of swollen joints	-14 (0.5)	-14 (0.5)	-3 (0.7)
Patient global – disease activity (VAS)	-25 (1.4)	-27 (1.5)	-4 (2.0)
Physician global – disease activity (VAS)	-35 (1.3)	-36 (1.3)	-9 (1.7)
Patient assessment of arthritis pain (VAS)	-24 (1.4)	-26 (1.4)	5 (1.9)
HAQ-DI	-0.5 (0.03)	-0.5 (0.03)	-0.1 (0.04)
CRP ratio to baseline (Geometric mean)	0.46	0.38	1.07
HAQ-DI responder (change ≤ -0.22)	152/246 (62%)	142/245 (58%)	14/127 (11%)
Change from baseline mTSS	n=214	n=222	n=127
Mean (SD)	0.2 (3)	-0.4 (2)	1.2 (4)
p-value (ANCOVA on ranks)	0.003	<0.001	
% Inhibition vs. Placebo+MTX	81%	134%	

Sources: Clinical Study Report Tables 11.12, 11.13, 11.14; SAS datasets

Study CDP870-011 (conducted 6/03 to 7/04)

Design

Study 11 was a randomized, double-blind, parallel arm, multi-center study. The objective was to evaluate the safety and efficacy of Cimzia in adult subjects with active rheumatoid arthritis who had failed at least one Disease Modifying Anti-Rheumatic Drug (DMARD). The double-blind treatment period was 24 weeks. The study was conducted in 36 sites in 3 countries (US, Czech Republic, Austria).

There were two treatment groups: Cimzia 400 mg SC administered every 4 weeks (q4w) and placebo. There was no concomitant MTX usage. This dose regimen of Cimzia monotherapy is the currently approved regimen for adults with Crohn's disease. The applicant has requested this as an alternative maintenance dose for RA. Patients received treatment at Week 0 (randomization) and every 4 weeks thereafter.

Eligible patients were 18 to 75 years old, diagnosed with adult-onset RA of at least six months duration, with active disease at screening and baseline. They also had to have failed at least one DMARD (either lack of efficacy or intolerance) and discontinued all DMARDS for a pre-specified length of time prior to enrollment.

As in studies 27 and 50, the primary efficacy measure was the ACR20 at Week 24, with all patients who discontinued considered as non-responders. The ACR50 and ACR70 endpoints, along with the individual components of the ACR scale were secondary endpoints. There was no x-ray data collected for this study.

Patient Disposition

Patients were adult males and females, ages 18 to 75, with active rheumatoid arthritis. A total of 220 patients were randomized to the study, 111 to the Cimzia treatment group and 109 to the placebo group. Table 8 shows the distribution of discontinuations by timepoint and reason.

In this study, there was no preplanned withdrawal for lack of efficacy in the protocol as in studies 27 and 50. As expected, there was a higher rate of discontinuations due to lack of efficacy in the placebo group. The two groups were similar in terms of the other reasons for discontinuation.

Table 8: Patient Disposition (Study 11)

	Cimzia 400 mg q4w	Placebo
Randomized	n=111	n=109
Total Discontinued	35 (32%)	81 (74%)
Discontinued		
Lack of Efficacy	24 (22%)	75 (69%)
Adverse Event	5 (5%)	2 (2%)
Non-compliance	4 (4%)	1 (1%)
Withdrew consent	2 (2%)	0
Lost to Follow-up	0	3 (3%)
Other	0	0
Completed	76 (69%)	28 (26%)

Source: Clinical Study Report Tables 10.2 and 10.3.

Baseline Demographics

The two treatment groups were fairly well balanced with respect to relevant demographic and baseline characteristics as shown in Table 9.

Table 9: Patient Demographics (Study 11)

	Cimzia 400 mg q4w n=111	Placebo n=109
Age (years)		
Mean (SD)	53 (13)	55 (12)
Range	21-80	28-79
Age categories:		
<65 yrs	88 (79%)	86 (79%)
≥65 yrs	23 (21%)	23 (21%)
Gender		
Female	87 (78%)	97 (89%)
Male	24 (22%)	12 (11%)

Race		
Caucasian	90 (81%)	87 (80%)
Hispanic/Latin Am.	0	0
African-American	13 (12%)	8 (7%)
Other	8 (7%)	14 (13%)
Weight (kg)		
Mean (SD)	76 (20)	80 (19)
BMI (kg/m^2)		
Mean (SD)	28 (7)	29 (7)
BMI categories:		
<25	43 (39%)	33 (31%)
25-29	33 (30%)	33 (31%)
≥30	35 (22%)	42 (39%)
Region		
United States	83 (75%)	82 (75%)
Czech/Austria	28 (25%)	27 (25%)

Sources: Clinical Study Report Tables 10.1, 11.1 and SAS datasets

Efficacy Results

For the responder endpoints, the protocol planned to compare the two treatment groups using a Cochran-Mantel-Haenzel (CMH) test with country as the stratification factor. This study was conducted in only three countries. As shown in Table 10, the result for the ACR 20 endpoint was statistically significant, in favor of Cimzia. All the results for the secondary endpoints were in the favorable direction to support the efficacy of the Cimzia monotherapy dose versus placebo. The Cimzia treatment group in this study received neither the dose level nor dosing schedule that the applicant is considering for initial treatment of signs and symptoms of adult RA, but it may be considered as a maintenance dose based on the Week 24 results.

Table 10: Efficacy Results (Study 11)

	Cimzia 400 mg q4w n=111	Placebo n=109
Primary Endpoint at Week 24		
ACR 20 (% responders)	50/111 45%	10/109 9%
Difference vs. placebo	36%	
p-value	<0.001	
Secondary Endpoints at Week 24		
ACR 50 (% responders)	25/111 (23%)	4/109 (4%)
ACR 70 (% responders)	6/111 (5%)	0 (0%)
ACR components [LS Mean Change from baseline (Std Dev)*]:		
Number of tender joints	-16 (17)	-7 (12)
Number of swollen joints	-12 (12)	-6 (8)
Patient global – disease activity (1 to 5)	-0.7 (1)	0 (1)
Physician global – disease activity (1 to 5)	-1.1 (1)	-0.2 (1)
Patient assessment of arthritis pain (VAS)	-21 (32)	2 (25)
HAQ-DI (0 to 3)	-0.4 (.7)	0.1 (.4)
CRP ratio to baseline (Geometric mean)	0.5	1.2
HAQ-DI responder (change ≤ -0.22)	70/111 (63%)	28/109 (26%)

Sources: Clinical Study Report Tables 11.9, 11.12, 14.2.4-9; SAS datasets
* Standard deviations are listed here because data was not provided to calculate the standard error for the LS Means.

Study CDP870-014 (conducted 10/02 to 1/04)

Design

Study 14 was a randomized, double-blind, parallel arm, multi-center study. The objective was to evaluate the safety and efficacy of Cimzia in adult subjects with active rheumatoid arthritis who were partial responders to methotrexate alone. The double-blind treatment period was 24 weeks. The study was conducted in 43 sites in the US and Europe.

There were two treatment groups: Cimzia 400 mg SC administered every 4 weeks (q4w) + MTX and placebo + MTX. All patients were on MTX at baseline. This dose regimen of Cimzia+MTX is not currently approved regimen for any indication, and is not a dose regimen the applicant has listed in the proposed label for adult RA. Patients received treatment at Week 0 (randomization) and every 4 weeks thereafter.

Eligible patients were 18 to 75 years old, diagnosed with adult-onset RA of at least six months duration, with active disease at screening and baseline. They also had to have received MTX for at least six months and been on a stable dose for at least 8 weeks prior to randomization. All other DMARD therapies must have been discontinued at least 4 weeks prior to randomization.

As in the other three studies, the primary efficacy measure for treatment of the signs and symptoms of RA was the ACR20 at Week 24, with all patients who discontinued considered as non-responders. The ACR50 and ACR70 responder endpoints, along with the individual components of the ACR scale were secondary endpoint. There was no x-ray data collected for this study.

The ITT population was defined as all randomized. The modified ITT population (mITT) was defined as all randomized patients who received at least 1 dose of study drug. Four patients, two in each treatment group, did not receive study drug and were dropped from the efficacy analyses.

Patient Disposition

Table 11 shows the distribution of patients who dropped by timepoint and reason. As in study 11, there was no per protocol criteria for discontinuing subjects who were not ACR responders at any time prior to Week 24. As expected, there was a difference in the rates of discontinuations due to lack of efficacy, but the two groups were similar in terms of the disposition reasons.

Table 11: Patient Disposition (Study 14)

	Cimzia 400 mg q4w +MTX	Placebo + MTX
Randomized	n=126	n=121
Randomized and received at least one dose of study drug (mITT)	124 (98%)	119 (98%)
Total Discontinued	28 (22%)	56 (46%)
Discontinued		
Lack of Efficacy	16 (13%)	45 (37%)
Adverse Event	7 (6%)	6 (5%)
Non-compliance	1 (1%)	0
Withdrew consent	2 (2%)	3 (2%)
Lost to Follow-up	0	0
Other	2 (2%)	2 (2%)
Completed	98 (78%)	65 (54%)

Source: Clinical Study Report Table 10.2

Baseline Demographics

The two treatment groups were well balanced with respect to relevant demographic and baseline characteristics as shown in Table 12.

Table 12: Patient Demographics (Study 14)

	Cimzia 400 mg q4w +MTX n=126	Placebo + MTX n=121
Age (years)		
Mean (SD)	53 (12)	56 (12)
Range	20-81	22-81
Age categories:		
<65 yrs	122 (84%)	94 (78%)
≥65 yrs	20 (16%)	26 (22%)

Gender Female Male	 91 (72%) 35 (28%)	 80 (67%) 40 (33%)
Race Caucasian Hispanic/Latin Am. African-American Other	 126 (100%) 0 0 0	 119 (98%) 0 0 2 (2%)
Weight (kg) Mean (SD)	 78 (16)	 79 (18)
BMI (kg/m^2) Mean (SD) BMI categories: <25 25-29 ≥30	 28 (6) 45 (36%) 40 (32%) 39 (31%)	 28 (5) 37 (31%) 48 (40%) 34 (29%)
Region United States Europe	 13 (10%) 113 (90%)	 12 (10%) 109 (90%)

Sources: Clinical Study Report Tables 10.1, 11.1 and SAS datasets

Efficacy Results

The efficacy analyses were the same for this study as for study 11. For the responder endpoints, the protocol planned to compare the two treatment groups using a CMH test with country as the stratification factor. This study was conducted in seven countries, with all countries having a minimum of five patients in each treatment group.

As shown in Table 13, the result for the ACR 20 endpoint was statistically significant, in favor of Cimzia. All the results for the secondary endpoints were in the favorable direction to support the efficacy of the Cimzia +MTX dose versus placebo. As in study 11, the Cimzia treatment group in this study received neither the dose level nor dosing schedule that the applicant is considering for initial treatment of signs and symptoms of adult RA. This dose regimen may be considered for maintenance in the label based on the Week 24 results.

Table 13: Efficacy Results (Study 14)

	Cimzia 400 mg q4w +MTX n=124	Placebo + MTX n=119
Primary Endpoint at Week 24		
ACR 20 (% responders)	56/124 45%	27/119 23%
Difference vs. placebo	22%	
p-value	<0.001	
Secondary Endpoints at Week 24		
ACR 50 (% responders)	22/124 (18%)	7/119 (6%)
ACR 70 (% responders)	0 (0%)	2/119 (2%)
ACR components [LS Mean Change from baseline (Std Dev)*]:	-15 (16)	-6 (16)
Number of tender joints	-13 (11)	-6 (11)
Number of swollen joints	-0.6 (1)	-0.3 (1)
Patient global – disease activity (1 to 5)	-1.1 (1)	-0.5 (1)
Physician global – disease activity (1 to 5)	-22 (26)	-9 (25)
Patient assessment of arthritis pain (VAS)	-0.3 (.5)	-0.1 (.4)
HAQ-DI (0 to 3)	0.6	0.9
CRP ratio to baseline (Geometric mean)		
HAQ-DI responder (change ≤ -0.22)	71/124 (57%)	35/119 (29%)

Sources: Clinical Study Report Tables 11.9, 11.12, 14.2.4-9; SAS datasets

* Standard deviations are listed here because data was not provided to calculate the standard error for the LS Means.

3.2 Evaluation of Safety

The safety profile of Cimzia was reviewed by Dr. Yancey.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

The applicant provided exploratory analyses for both primary endpoints by age groups, gender, and race. The analyses are for descriptive purposes only and are presented in Table 14. There were no notable differences in the responder rates for the treatments across any of these subgroups.

Table 14: Primary Efficacy Results by Subgroups

Primary endpoint: ACR 20 % Responders n/N (%)	Age		Gender		Race	
	<65 yrs	≥65 yrs	Female	Male	Caucasian	Non-Caucasian
Study 27						
Cimzia 200 q2w + MTX	194/337 (58)	34/51 (67)	186/321 (58)	42/67 (63)	209/359 (58)	19/29 (66)
Cimzia 400 q2w + MTX	206/330 (62)	30/58 (52)	200/324 (62)	36/64 (56)	209/347 (60)	27/41 (66)
Placebo + MTX	25/172 (15)	2/26 (8)	24/166 (15)	3/32 (9)	21/179 (12)	6/19 (32)
Study 50						
Cimzia 200 q2w + MTX	123/213 (58)	18/33 (55)	123/206 (60)	18/40 (45)	138/239 (58)	3/7 (43)
Cimzia 400 q2w + MTX	117/203 (58)	24/42 (57)	112/191 (59)	29/54 (54)	138/241 (57)	3/4 (75)
Placebo + MTX	8/112 (7)	3/15 (20)	11/107 (10)	0/20 (0)	11/126 (9)	0/1 (0)
Study 11						
Cimzia 400 q4w	44/87 (51)	6/23 (26)	36/87 (41)	14/23 (61)	39/90 (43)	11/21 (52)
Placebo	8/85 (9)	2/23 (9)	8/97 (8)	2/11 (18)	8/87 (9)	2/22 (9)
Study 14						
Cimzia 400 q4w + MTX	49/103 (48)	7/19 (37)	38/90 (42)	18/32 (56)	55/124 (44)	0/0
Placebo + MTX	20/93 (22)	7/25 (28)	16/80 (20)	11/38 (29)	28/118 (24)	0/2

Source: Study Report Tables 14.2.1.6-9

4.2 Other Special/Subgroup Populations

Dr. Yancey requested subgroup analyses by geographical region. The regions were classified differently in the studies, as shown in the column headings in Table 15. These are descriptive only, and do not show any notable differences across the groups.

Table 15: Primary Efficacy Results by Region

Primary endpoint: ACR 20 % Responders n/N (%)	Two Regions (categories for studies 11 and 14)		Four Regions (categories for studies 27 and 50)			
	United States	Europe	Central/ South America	Eastern Europe	Russia/ Baltic/ Scand.	Rest of World (incl US)
Study 27						
Cimzia 200 q2w + MTX			38/60 (63)	84/140 (60)	69/122 (57)	37/66 (56)
Cimzia 400 q2w + MTX			45/63 (71)	86/136 (63)	73/121 (60)	32/68 (47)
Placebo + MTX			10/30 (33)	9/71 (13)	4/62 (6)	4/35 (11)
Study 50						
Cimzia 200 q2w + MTX				65/118 (55)	63/98 (64)	13/30 (43)
Cimzia 400 q2w + MTX				72/123 (59)	59/101 (58)	10/21 (48)
Placebo + MTX				7/61 (11)	2/53 (4)	2/13 (15)
Study 11						
Cimzia 400 q4w	39/90 (33)	13/28 (46)				
Placebo	6/82 (7)	4/27 (15)				
Study 14						
Cimzia 400 q4w + MTX	4/13 (31)	51/113 (45)				
Placebo + MTX	4/12 (33)	24/109 (22)				

Source: SAS datasets for ISE

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

In all four studies the placebo group experienced the highest discontinuation rates due to lack of efficacy, but this was expected, particularly in studies 27 and 50 which included a protocol requirement to drop non-responders midway through the 24 week double-blind treatment period. Other than that, the number and reasons for discontinuations were not unbalanced. The primary efficacy endpoint in all four studies was the ACR20, a binary responder endpoint. All patients who discontinued for any reason were classified as non-responders for the primary analyses, so the dropouts were appropriately reflected in the results.

Different dose levels and dosing schedules for Cimzia were tested among the four studies reviewed here. Two of the studies, 27 and 50, provide direct evidence to support the dose regimen selected by the applicant: 200 mg q2w (following a loading dose of 3x400 q2w) + MTX. In the other two studies, 11 and 14, the dose level was higher (400 mg) and the dosing schedule was longer (q4w). The higher dose may be considered for maintenance in the label.

The models and analyses used were appropriate for the study designs. In all primary comparisons, the Cimzia treatment group was statistically significantly better than the comparable placebo treatment group. Based on the results of studies 27 and 50, there is sufficient evidence to support the efficacy of Cimzia 200 mg q2w (following a loading dose of 3x400 q2w) + MTX for the treatment of RA in adults.

5.2 Label Issues

The applicant's proposed label reports the results from the analyses in the Clinical Studies section. The proposed label presents information from studies 27 (referred to as RA-I), 50 (RA-II), and 11 (RA-III). Studies 27 and 50 included the dose regimen proposed for treatment of adults with active RA: 200 mg q2w (following a loading dose of 3x400 q2w) + MTX. It is appropriate for these two studies to appear in the RA clinical studies section.

Study 11 had the 400 mg q4w dose Cimzia dose with no MTX in the regimen. This is the monotherapy dose which is currently approved for treatment of Crohn's disease, but is not the dose planned for RA patients. Since study 11 dose not include the planned dose for RA patients, I would prefer the RA clinical study results be removed from the clinical studies section to avoid confusion with the Crohn's treatment regimen. That change would affect the text, and Tables 3 and 5. The label does not include the efficacy results for study 14, which included the 400 mg q4w dose + MTX regimen.

(b) (4)

. The proposed label also reports additional endpoints for physical function and patient report outcomes in paragraphs after the main results. These should be excluded. Lastly, the paragraph which accompanies Figure 1, which shows the ACR 20/50/70 results at each timepoint in the 52-week study, should be removed. It describes significant differences as early as week 1, which were not preplanned comparisons to support label claims.

5.3 Conclusions and Recommendations

Based on the results of studies 27 and 50, there is sufficient evidence to conclude that Cimzia 200 mg q2w (following a loading dose 3x400 mg q2w) + MTX is statistically better than placebo + MTX for the treatment of RA as measured by the signs and symptoms using the ACR20 at

Week 24. In addition, the single 52-week study provided evidence of efficacy for inhibition of structural damage. A 24-week study provided supportive evidence for the structural damage indication.

Signatures/Distribution List Page

Katherine B. Meaker, M.S.
Mathematical Statistician

8/28/08

Dionne Price, Ph.D.
Team Leader

8/28/08

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA: 125271	Submission Date(s): 11/29/2007
Brand Name	Cimzia
Generic Name	Certolizumab Pegol Injection
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Pharmacometrics Reviewer	Christoffer W. Tornoe, Ph.D.
Pharmacometrics Team Leader	Joga Gobburu, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Rheumatology Products
Sponsor	UCB, Inc.
Relevant IND(s)	9,869 and 11,917
Formulation; Strength(s)	Liquid in Pre-filled Syringe for Subcutaneous Injection; 200 mg/mL
Indication	Treatment of adults with active rheumatoid arthritis
Proposed Dosage Regimen	400 mg at weeks 0, 2, and 4 followed by 200 mg every other week. Alternatively 400 mg every 4 weeks can be considered as a maintenance dose.

Table of Contents

Concurrence:

Srikanth C. Nallani, Ph.D. 8/15/2008

Christoffer W. Tornoe, Ph.D. 8/15/2008

Joga Gobburu, Ph.D. 8/19/2008

Suresh Doddapaneni, Ph.D. 8/15/2008

1. Executive Summary

1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, the information contained in this submission is acceptable, provided that
a) The sponsor accepts the Post Marketing commitment stated below; and
b) A mutually acceptable agreement can be reached between the Agency and sponsor regarding the language in the package insert.

1.2 Phase IV Commitments

PK/PD studies in pediatric patients, diagnosed with Juvenile Rheumatoid Arthritis (JRA), should be conducted with a focus on developing optimal dosing regimen for further clinical evaluation.

1.3 Summary of Clinical Pharmacology Findings

UCB Inc., submitted BLA 125271 for approval to market Cimzia, certolizumab pegol (also referred as certolizumab or CDP-870), for the treatment of adults with active rheumatoid arthritis. Cimzia is approved for the treatment of Crohn's disease on April 22, 2008.

The dosing regimen proposed for treatment of RA is as follows:

1) 400 mg at weeks 0, 2, and 4 followed by a maintenance dose of 200 mg every other week.

2) Alternatively 400 mg every 4 weeks can be considered as a maintenance dose.

The Clinical Pharmacology studies supporting dosing or other claims include:

a) Four healthy volunteer studies (CDP870-001, CDP870-003, PHA-024 and CDP870-038), and 1 study of the pharmacokinetics (PK) of certolizumab in subjects with RA receiving methotrexate (MTX) (PHA-001).

b) A phase II dose finding study (CDP870-004) that evaluated dose levels of 50, 100, 200, 400, 800 mg sc certolizumab q4w versus placebo. In this clinical study, RA patients did not receive methotrexate as concomitant medication.

c) Initial phase III safety and efficacy studies in subjects with RA (CDP870-011 and CDP870-014) used a dose schedule of 400 mg every 4 weeks (Q4W). Note that these two studies were conducted without the loading infusion proposed; and RA patients received methotrexate only in study #014.

d) Later phase III studies in subjects with RA on methotrexate (CDP870-027 and CDP870-050) used a loading dose regimen of 400 mg sc certolizumab or placebo given on Weeks 0, 2 and 4, followed by either 400 mg or 200 mg certolizumab or placebo every 2 weeks (Q2W). The 400 mg Q2W loading dose regimen at Weeks 0, 2, and 4 was based on the dose regimen used for induction of response in phase III studies subjects with CD (CDP870-031 and CDP870-032) and was supported by 2 pharmacokinetic modeling and simulation analyses.

A population PK/PD exposure-response analysis of data from above indicated studies established relationship between certolizumab concentrations at steady-state and efficacy for the treatment of subjects with RA. The exposure-response analysis addressed the following key points:

1) Dose-response and Concentration-response supporting the clinical efficacy of certolizumab dosing regimen proposed

2) Dose-response or concentration response supporting clinical safety of proposed certolizumab dosing regimen

3) Benefit of the proposed loading dose infusion (400 mg q2w at weeks 0, 2 & 4)

A) Exposure-Response Analysis:

1) Dose-response and Concentration-response supporting the clinical efficacy of certolizumab dosing regimen proposed

Dose-Response:

RA patients (n=40) in Phase II dose-ranging study #004 were treated with certolizumab (Panel 1: Placebo, 50 – 400 mg, Panel 2: Placebo, 600 – 800 mg) q4w for 12 weeks in a double-blind, placebo-controlled fashion. Patients in this study did not receive methotrexate. The primary measure of efficacy was the number of certolizumab-treated patients who had a 20% improvement in disease activity (ACR 20) at Week 12 versus placebo-treated patients. In Panel 1, a significantly greater proportion of patients achieved an ACR-20 response at Week 12 in the CDP-870 400 mg treatment group as compared to placebo or CDP-870 50, 100 or 200 mg treatment groups. In panel 2, both 600 and 800 mg q4w regimen had more patients responding to treatment.

Table: ACR20 response by week following certolizumab administration.

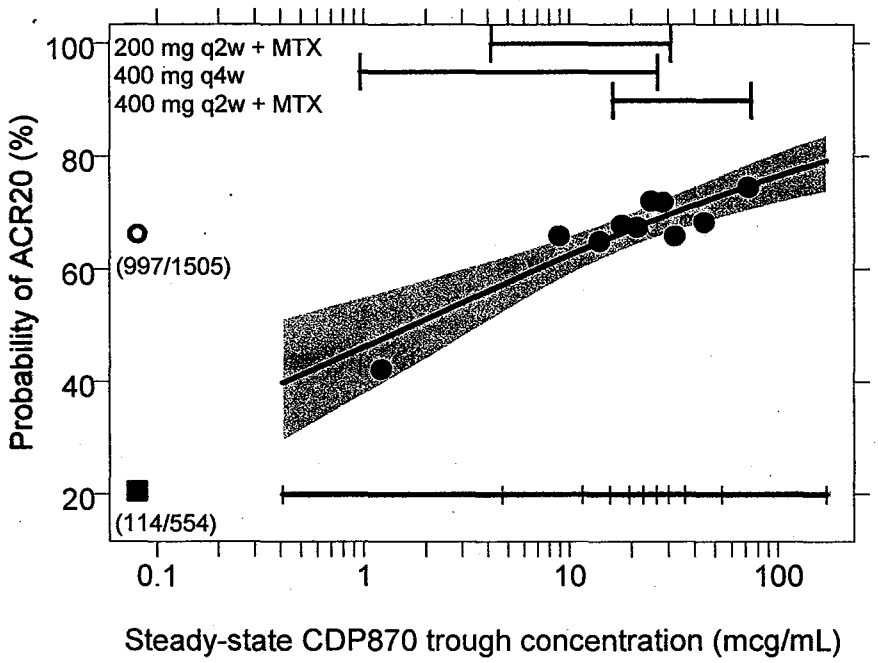
Treatment	Panel 1					Panel 2		
	Placebo	CDP-870 50 mg	CDP-870 100 mg	CDP-870 200 mg	CDP-870 400 mg	Placebo	CDP-870 600 mg	CDP-870 800 mg
N	40	39	40	41	42	44	39	38
Week 1	3	31*	23*	44*.	45*	9	49*	53*
Week 4	15	31	28	51*.	48*	12	59*	74*
Week 8	13	23	40*	39*	64*.	19	67*	66*
Week 12	15	21	20	34	60*.	19	64*	79*

* p< 0.05 versus placebo within the panel; . p<0.05 versus CDP-870 50, 100 and 200 mg; . p <0.05 versus CDP-870 100 mg.

Efficacy was noted as early as week 1 but only 400 mg treatment group had a sustained response up to week 12; while the 600 and 800 mg treatments did not result in greater response.

Concentration-Response:

There is clear evidence of exposure-response relationship for effectiveness (ACR-20 at week 24) for certolizumab using steady-state certolizumab trough concentrations (C_{trough}) on the log scale as the exposure variable (see figure below).



The overall ACR-20 response rate for placebo and certolizumab treated patients was 20% and 66%. Patients with C_{trough} > 10 mcg/mL had ACR-20 response rates above the overall response rate of 66%. The only dosing regimen that results in more than 90% of patients (antibody positive and negative) with C_{trough} > 10 mcg/mL is 400 mg q2w + MTX whereas 90% of patients receiving 400 mg q4w (- MTX) or 200 mg q2w + MTX had C_{trough} above 4 and 1 mcg/mL, respectively. For antibody negative patients only, the 10^{th} C_{trough} percentile for 400 mg q4w, 200 mg q2w +MTX, and 400 mg q2w + MTX is 3, 7, and 18 mcg/mL, respectively.

2) Dose-response or concentration response supporting clinical safety of proposed certolizumab dosing regimen

There is an increase in risk for infection in patients receiving Cimzia, as compared with patients receiving placebo. However, the risk of infection was not dose-related. In addition, there was no significant difference in the incidence of infections between the MTX and non-MTX RA patients.

Exposure-safety relationships were identified for infections as well as high level terms: Upper and lower respiratory tract, urinary, and herpes viral infections in studies 004, 011, 014, 027, 050 using C_{max} concentrations as a measure of exposure. However, dose adjustments are not warranted since most infections were non-serious and easily resolved when treated.

3) Benefit of the proposed loading dose (400 mg q2w at weeks 0, 2 and 4)

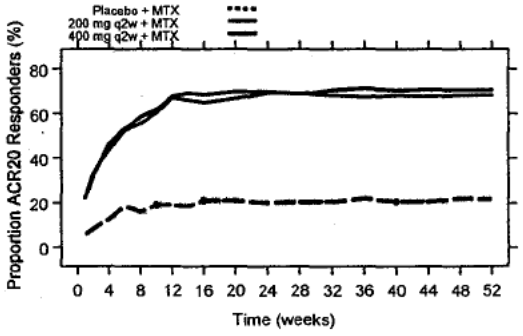
The proposed loading certolizumab dose has been investigated in two adequate well controlled studies (#027 and #050) in conjunction with the 200 mg q2w maintenance dose as well as higher maintenance dose 400 mg q2w. However, the proposed alternate maintenance dose of 400 mg q4w was evaluated in adequate well controlled studies (#011 and #014) and demonstrated efficacy without the loading dose. The following discussion will address the benefit of adding the loading dose with the alternate maintenance dose.

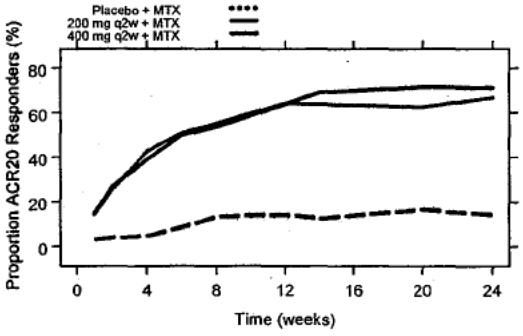
The primary endpoint ACR20 response rates observed across dose groups at week 24 from the four confirmatory trials are summarized in the table below. As such the proposed maintenance dose of 400 mg q4w is efficacious in treating RA. The ACR-20 response rates increased from 50 to 70% when giving a loading dose and shifting from q4w to q2w dosing.

Table: ACR-20, ACR-50, and ACR-70 response rates for different dosing regimens tested in studies # 011, #014, #027, and #050.

Week 24	Placebo	Placebo + MTX	400 mg q4w	400 mg q4w +MTX	200 mg q2w +MTX	400 mg q2w +MTX
ACR-20	15%	20%	50%	50%	68%	70%
ACR-50	5%	7%	23%	19%	38%	40%
ACR-70	0%	2%	5%	0%	21%	18%

Steady-state certolizumab levels are noted around 4 weeks whereas the ACR-20 response is at steady-state around 12 weeks after initiation of CDP870 treatment (see Figures below). It is thus difficult to separate out the effectiveness benefit of administering a loading dose of 400 mg q2w at weeks 0, 2, and 4 since the maintenance dose was also changed from 400 mg q4w in studies 011 and 014 to 200/400 mg q2w in studies 027 and 050.





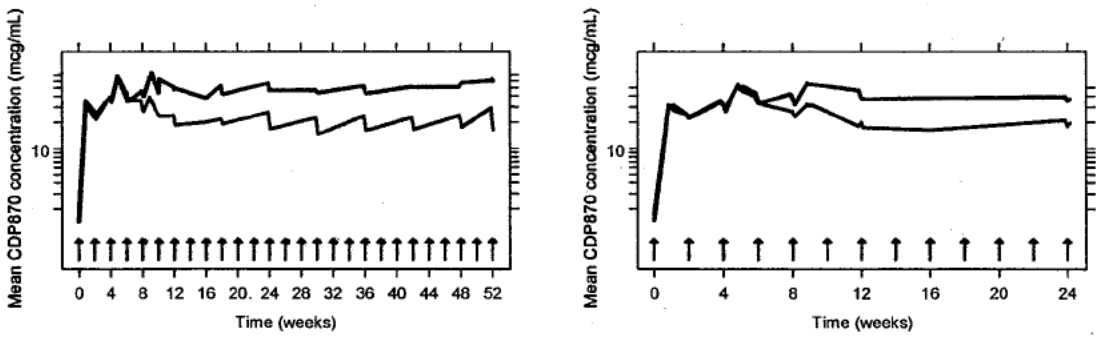


Figure Legend. Proportion ACR-20 responders (top) and mean CDP870 concentration (bottom) time profiles for study 027 (left) and 050 (right). The ACR-20 response reaches steady-state around 12 weeks after initiation of treatment with the PK reaching levels above steady-state.

However, predictions based on sponsor's PK/PD model showed that a loading dose would result in a typical 9% improvement in the probability of achieving an ACR 20 response rate at Week 12 following initiation of treatment compared with a non-loading dose regimen of 200 mg q2w. At Week 22, the predicted difference between the loading dose and the non-loading dose regimens was reduced to a 3% improvement in the probability of achieving an ACR 20 response. These predictions suggest that the main effectiveness benefit of the loading dose regimen is an improvement in speed of onset of ACR response predicted for the individual subject. Furthermore, the probability of developing antibodies was found to decrease with increasing concentrations and was also found to be irreversible thus supporting loading the subjects with higher doses to reduce the probability of developing antibodies.

B) Pharmacokinetics of Certolizumab:

PK of certolizumab was investigated in the range of 1 – 50 mg/kg (50 – 800 mg fixed dose) in healthy volunteers and RA patients following intravenous and subcutaneous administration. PK of certolizumab was similar in healthy volunteers and RA patients. Mean clearance (CL) values of 0.13 - 0.20 ml/hr/kg indicated that certolizumab is a low clearance drug with a mean terminal phase half-live of 13 – 15 days. The volume of distribution was similar to total blood volume (60 – 102 ml/kg) and suggest that the majority of certolizumab in the body is restricted mainly to the blood. Bioavailability of certolizumab is about 80% following subcutaneous administration.

Intrinsic and extrinsic factors affecting certolizumab PK and clinical response

Population PK analysis evaluated the effect of age, body weight, race, gender, anti-certolizumab antibody status, concomitant medications (methotrexate, glucocorticoids, NSAIDs, other DMARDs) and laboratory assay on the PK of certolizumab.

Only body weight and antibody status were identified as covariates for clearance in sponsor's population PK analysis with the latter being the major contributor to variability in clearance (see Figures below). However, fixed dosing, i.e. not body weight corrected dosing, is appropriate since the probability of ACR-20 response is similar (~70%) across

all body weight quartiles due to the shallow body weight – C_{trough} relationship and high enough exposures at the proposed dosing regimen.

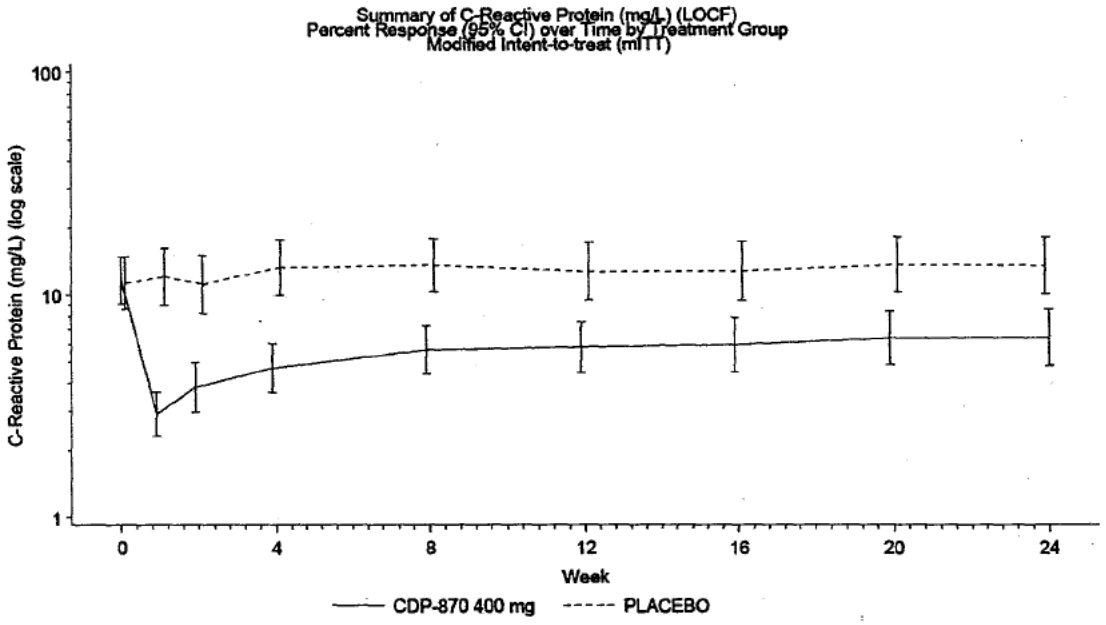
Effect of anti-certolizumab antibodies on certolizumab PK, PD and clinical response

The presence of anti-certolizumab antibodies had the most significant effect on the PK of certolizumab. The population PK analysis showed that antibodies increased the clearance of certolizumab by 3-fold. The increase in certolizumab clearance caused by antibodies results in a 46 % reduction in C_{max}, 82 % reduction in C_{trough}, and 60 % reduction in AUC for the dose interval. Body weight was found to have an effect of ±20% on C_{max}, ±50% on C_{trough}, and ±30% on AUC.

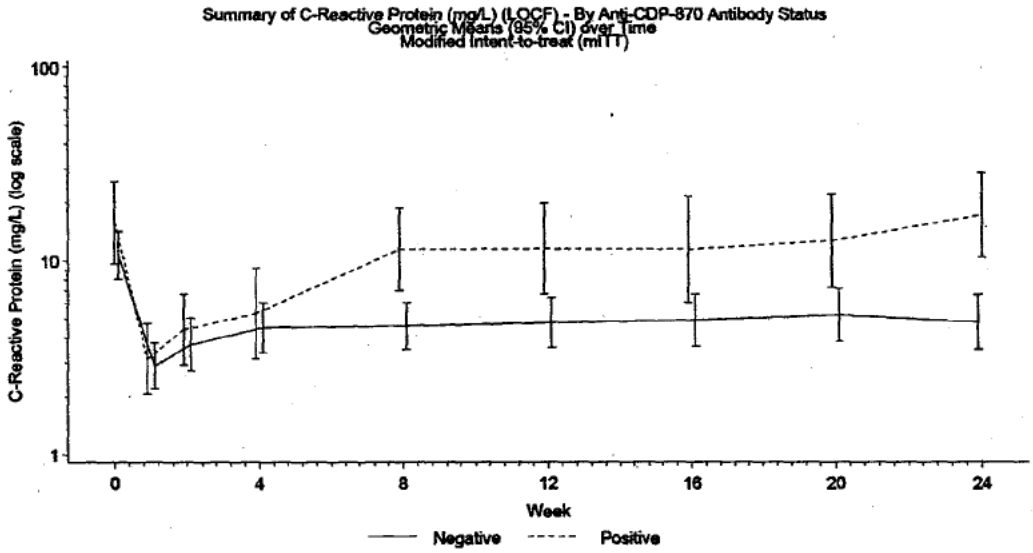
Figure Legend. (Left) Clearance vs. body weight for antibody negative (black circles) and positive (red crosses) patients with population predictions (red lines). **(Right)** Box plot of individual predicted clearances for antibody negative and positive patients together with population predictions (red lines).

Compared to anti-certolizumab antibody negative RA patients, antibody positive patients produced a lower ACR 20 response and a lower pharmacodynamic response (CRP levels).

C-reactive protein (CRP) levels, indicator of inflammation, were measured as a pharmacodynamic endpoint and as a clinical response endpoint in most clinical studies. Significant decrease in CRP levels was noted immediately after treatment initiation with certolizumab compared to placebo (see figure below).



While in RA patients treated with certolizumab CRP levels increased upon development of antibodies by weeks 4 and later, CRP levels remained low in antibody negative patients (see figure below).



Studies #027 and #050 evaluated efficacy of certolizumab in RA patients on stable doses of methotrexate. Among 393 RA patients receiving 200 mg q2w regimen 10.8% were antibody positive. These patients had lower ACR20 response (50 % response) compared to antibody negative patients (60% response). Subgroup analysis testing ACR20 results against antibody status of the RA patient revealed that percentage of ACR20 responders was reduced in the antibody positive patients (See tables below).

Table: Comparison of the ACR20 Response by Antibody Status at Week 24 – ITT Population (Study CDP870-027)

Week 24	**Certolizumab 200 mg + MTX (N = 393)**		**Certolizumab 400 mg + MTX (N = 390)**	
	Ab+	Ab-	Ab+	Ab-
n (%)	42 (10.8%)	346 (89.2%)	8 (2.1%)	380 (97.9%)
Responder	20 (47.6%)	208 (60.1%)	4 (50%)	232 (61.1%)
Non-Responder	22 (52.4%)	138 (39.9%)	4 (50%)	148 (38.9%)

Table: Comparison of the ACR-20 Responder Rate by Antibody Status at Week 24 – ITT Population (Study CDP870-050)

Week 24	**Certolizumab 200 mg + MTX (N = 246)**		**Certolizumab 400 mg + MTX (N = 246)**	
	Ab+	Ab-	Ab+	Ab-
n (%)	20 (8.1%)	226 (91.9%)	4 (1.6%)	241 (98.0%)
Responder	7 (35.0%)	134 (59.3%)	2 (50.0%)	139 (57.7%)
Non-Responder	13 (65.0%)	92 (40.7%)	2 (50.0%)	102 (42.3%)

Taken together, anti-certolizumab antibody formation significantly affects certolizumab PK, PD and clinical response. Concomitant use of methotrexate decreases the anti-certolizumab antibody formation. Hence, the alternative proposed maintenance dose regimen of 400 mg q4w without MTX is not appropriate because:

- Shifting from 200 mg q2w to 400 mg q4w dosing (same monthly dose) will result in lower ACR-20 response rates due to lower C_{trough} (ACR-20 response rate of 70% for q2w dosing compared to 50% for q4w dosing).
- Shifting from co-administration of MTX to monotherapy will increase the antibody formation from 6% to 20% resulting in lower probability of ACR-20 response due to lower C_{trough}.

Overall, the clinical pharmacology submission is acceptable. Given the well characterized exposure-response and clinical efficacy in adult RA patients, certolizumab may make an addition to the available treatment armamentarium for Juvenile Rheumatoid Arthritis. The established exposure-response information in adults combined with pediatric PK/PD information might help with the selection of an optimal certolizumab dose for conducting adequate well controlled clinical efficacy studies in JRA patients. Hence, the sponsor's should conduct post marketing studies to evaluate the PK/PD of certolizumab in JRA patients.

2 QBR

2.1 General Attributes

UCB Inc., submitted a BLA for approval to market Cimzia, certolizumab pegol, for the treatment of adults with active rheumatoid arthritis. Sponsor's BLA 125160 was approved by the FDA for the treatment of active Crohn's disease as of 4/22/2008. The proposed commercial formulation is a solution in a pre-filled syringe intended for self-administration. Cimzia formulation approved for use in Crohn's disease was a sterile, white, lyophilized powder for reconstitution.

Proposed Mechanism of Action in RA: Certolizumab pegol (CDP870) is an engineered, humanized, antibody Fab' fragment with specificity for human TNFα, which is manufactured in E. coli. The Fab' fragment is subsequently purified and conjugated to polyethylene glycol (PEG). Studies to date have demonstrated that certolizumab pegol is an effective inhibitor of TNFα, a polypeptide cytokine known to mediate the up-regulation of cellular adhesion molecules and chemokines, up-regulation of major histocompatibility complex (MHC) class I and class II molecules, and direct leukocyte activation, in rheumatoid arthritis (RA).

Dosage and Administration for treatment of adults with active rheumatoid arthritis: 400 mg at weeks 0, 2, and 4 followed by 200 mg every other week. Alternatively 400 mg every 4 weeks can be considered as a maintenance dose.

2.2 General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies supporting the dosing regimen and other claims?

The Clinical Pharmacology studies supporting dosing or other claims include 4 healthy volunteer studies (CDP870-001, CDP870-003, PHA-024 and CDP870-038), and 1 study of the pharmacokinetics (PK) of CZP in subjects with RA receiving methotrexate (MTX) (PHA-001). Clinical studies investigating the efficacy of CZP in RA that provided pharmacokinetic and pharmacodynamic data include the studies in the table below. The table also includes details of clinical and clinical pharmacology studies with regard to number of subjects, controls employed, PK and PD sampling.

Study number	Type	Subject N° total/active Population	Route, Dose and Formulation	Control Population	PK Sampling	PD sampling
004	Therapeutic exploratory	320/239	sc: 2 panels:0, 50, 100, 200, 400 or 600, 800 mg, Q4wk dosing, liquid formulation 200 mg/mL (b) (4)	Placebo	Weeks 0, 1, 2, 4, 5, 6, 8, 9, 10 and 12, pre-dose and 4, 12 and 18 week	Baseline and at Week 1, 2, 5, 6, 8, 9, 10 and 12
011	Therapeutic confirmatory	219/111	sc: 0, 400 mg, Q4wk dosing, Lyophilized powder	Placebo	Weeks 0, 1, 2, 4, 8, 12, 16, 20, 21, 22 and 24, then 4 and 12 weeks after the last dose	Baseline and at Week 1, 2, 4, 8, 12, 16, 20 and 24

014	Therapeutic confirmatory	243/124	sc: 0, 400 mg, Q4wk dosing, Lyophilized powder	Placebo + methotrexate	Weeks 0, 1, 2, 4, 8, 12, 16, 20, 21, 22 and 24, then 12 weeks after the last dose	Baseline and at Week 1, 2, 4, 12, 16, 20 and 24
027	Therapeutic confirmatory	979/780	sc: 0, 200, 400 mg, Q2wk dosing, Lyophilized powder (200 mg Q2W was following an initial regimen of CZP 400 mg at Baseline, Week 2 and Week 4)	Placebo + methotrexate	Weeks 0 (pre-dose), 1, 2, 4, 5, 6, 8, 9, 10, 12, 18, 24, 30, 36, 42, 48 and 52, then 12 weeks after the last dose	Baseline and at Week 1, 2, 4, 6, 8, 9, 10, 12, 14, 16, 20, 24, 28, 32, 36, 40, 44 and 48
050	Therapeutic confirmatory	619/493	sc: 0, 200, 400 mg, Q2wk dosing liquid formulation 200 mg/mL (pH 4.7) (200 mg Q2W was following an initial regimen of CZP 400 mg at Baseline, Week 2 and Week 4)	Placebo + methotrexate	Weeks 0 (pre-dose), 1, 2, 4, 5, 6, 8, 9, 12, 24 and at the 12 week follow up visit	Baseline and at Week 1, 2, 4, 6, 8, 12, 14, 16, 20 and 24

2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The primary measure of efficacy was the widely accepted "ACR-20" Responder Rates at Week 12. American College of Rheumatology (ACR) defines a patient as an "ACR-20" responder if:

1. The counts for both tender and swollen joints have reduced by 20% or more; and
2. Three of the following five assessments show a reduction of 20% or more in Baseline assessment:

a. Patient's Assessment of Pain
b. Patient's Global Assessment of Disease Activity
c. Physician's Global Assessment of Disease Activity
d. HAQ-DI
e. Acute phase reactant (either CRP or ESR)

3. Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Sponsor evaluated certolizumab in plasma from a variety of Clinical/Clinical Pharmacology Studies employing validated analytical methods. Please refer to the Analytical Section below for details of validation for the methods.

4. Exposure-response

a) What are the characteristics of the exposure-response relationships for efficacy?

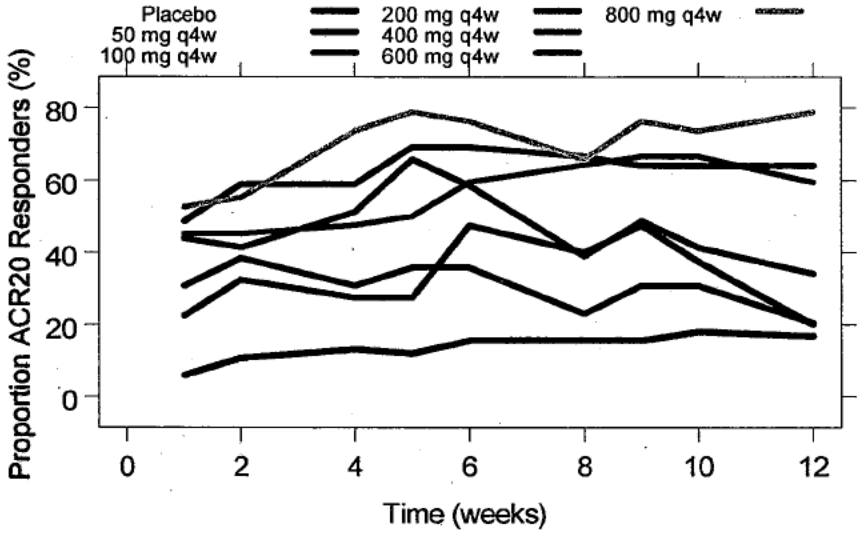
Dose-related increase in ACR20 response in RA patients treated with different regimen of certolizumab was noted across different clinical studies.

In addition, ACR20 response improved with increase in certolizumab concentrations (trough) at steady-state. The overall ACR-20 response rate for placebo and certolizumab treated patients was 20% and 66%. Patients with C_{trough} > 10 mcg/mL had ACR-20 response rates above the overall response rate of 66%.

Loading infusion dose (400 mg q2w at weeks 0, 2 and 4 weeks) produces a faster ACR20 responder status in RA patients. However, the effect of the loading infusion does not last beyond 12 weeks of treatment.

Dose-Response across different studies:

Excerpts from the pharmacometric analysis of PK-PD data conducted by Dr. Christoffer Tornoe are presented here. A clear dose-response relationship at week 12 is seen in the initial dose-ranging study # 004 with doses from 50 – 800 mg q4w without concomitant methotrexate (MTX) (see figure below).



Proportion ACR-20 responders over time in the dose-finding study # 004 with doses ranging from 50-800 mg q4w without concomitant MTX.

The dose of 400 mg q4w was selected for the initial confirmatory studies # 011 (without MTX) and # 014 (with MTX). Although both studies met their primary endpoint with the 400 mg q4w regimen, two additional clinical studies #027 and #050 were conducted with regimen employing more frequent certolizumab administration, i.e., 200 q2w & 400 q2w along with methotrexate. The 200 mg q2w dose was preceded by a loading infusion of 400 mg q2w at weeks 0, 2 and 4 in study #027 and #050.

The ACR-20 response rates across dose groups at week 24 from the four confirmatory trials are summarized in the table below. The ACR-20 response rates increased from 50 to 70% when giving a loading dose and shifting from q4w to q2w dosing.

Table: ACR-20, ACR-50, and ACR-70 response rates for different dosing regimens tested in studies # 011, #014, #027, and #050.

Week 24	Placebo	Placebo	400 mg q4w	400 mg q4w	200 mg q2w	400 mg q2w

		+ MTX		+MTX	+MTX	+MTX
ACR-20	15%	20%	50%	50%	68%	70%
ACR-50	5%	7%	23%	19%	38%	40%
ACR-70	0%	2%	5%	0%	21%	18%

ACR20 response with respect to plasma certolizumab concentrations (trough) at steady-state:

There is clear evidence of exposure-response relationship for effectiveness (ACR-20 at week 24) for certolizumab using steady-state certolizumab trough concentrations (C_{trough}) on the log scale as the exposure variable (see figure below).

The overall ACR-20 response rate for placebo and certolizumab treated patients was 20% and 66%. Patients with C_{trough} > 10 mcg/mL had ACR-20 response rates above the overall response rate of 66%. The only dosing regimen that results in more than 90% of patients (antibody positive and negative) with C_{trough} > 10 mcg/mL is 400 mg q2w + MTX whereas 90% of patients receiving 400 mg q4w (- MTX) or 200 mg q2w + MTX had C_{trough} above 4 and 1 mcg/mL, respectively. For antibody negative patients only, the 10th C_{trough} percentile for 400 mg q4w, 200 mg q2w +MTX, and 400 mg q2w + MTX is 3, 7, and 18 mcg/mL, respectively.

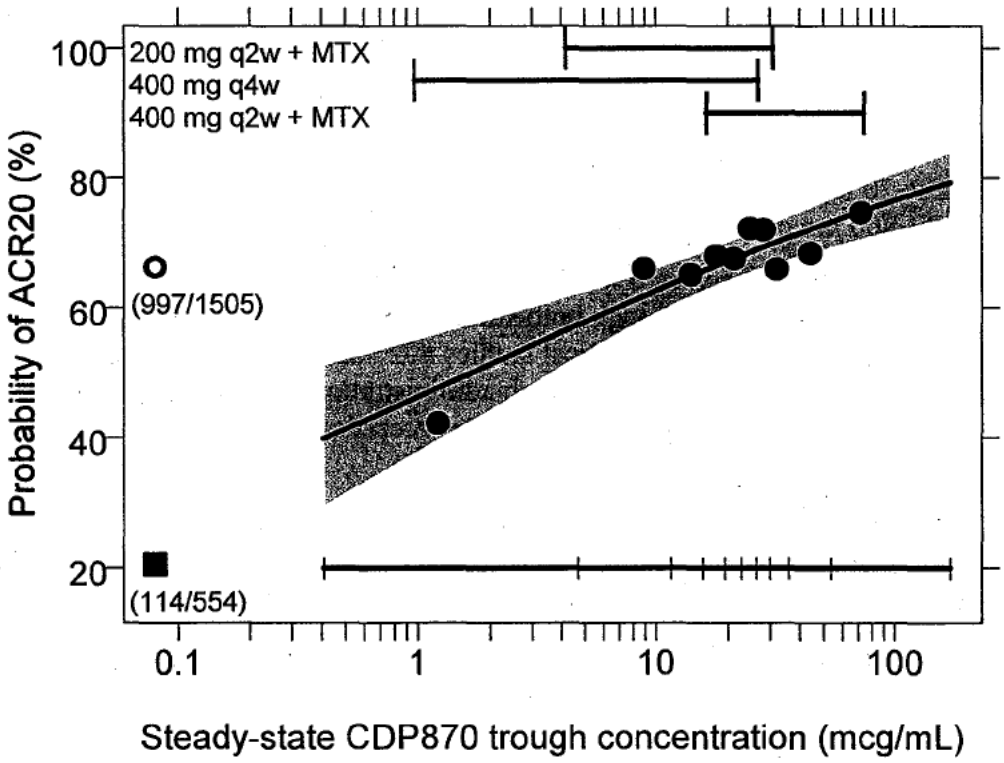


Figure Legend: Exposure-response relationship for effectiveness at primary endpoint. Probability of ACR-20 response vs. steady-state certolizumab trough concentrations ($C_{ss,trough}$) at week 24 for studies 011, 014, 027, and 050. The overall certolizumab treated (open red circle) and placebo (solid black square) response rates are shown at the left hand side. The solid black line is the predicted ACR-20 response rate from the lowest to highest observed $C_{ss,trough}$ and the associated 95% CI (shaded area). The red dots represent the median $C_{ss,trough}$ in each decatile and the associated observed ACR-20 (LOCF) response rate. The colored horizontal bars represent the 10-90th certolizumab steady-state trough concentration percentiles for 200 mg q2w + MTX (orange), 400 mg q4w (blue), and 400 mg q2w + MTX (brown).

Is the loading dose appropriate?

Sponsor has evaluated the safety and efficacy of 200 mg q2w regimen (Studies #027 and #050) with an initial loading infusion of 400 mg q2w at weeks 0, 2 and 4. However, use of this loading infusion is proposed with the alternative regimen of 400 mg q4w, although it was not evaluated in clinical trials (Studies # 011 and #014). The following discussion addresses the benefit of the proposed loading dose.

Steady-state certolizumab levels are noted around 4 weeks whereas the ACR-20 response is at steady-state around 12 weeks after initiation of CDP870 treatment (see Figures below). It is thus difficult to separate out the effectiveness benefit of administering a loading dose of 400 mg q2w at weeks 0, 2, and 4 since the maintenance dose was also changed from 400 mg q4w in studies 011 and 014 to 200/400 mg q2w in studies 027 and 050.

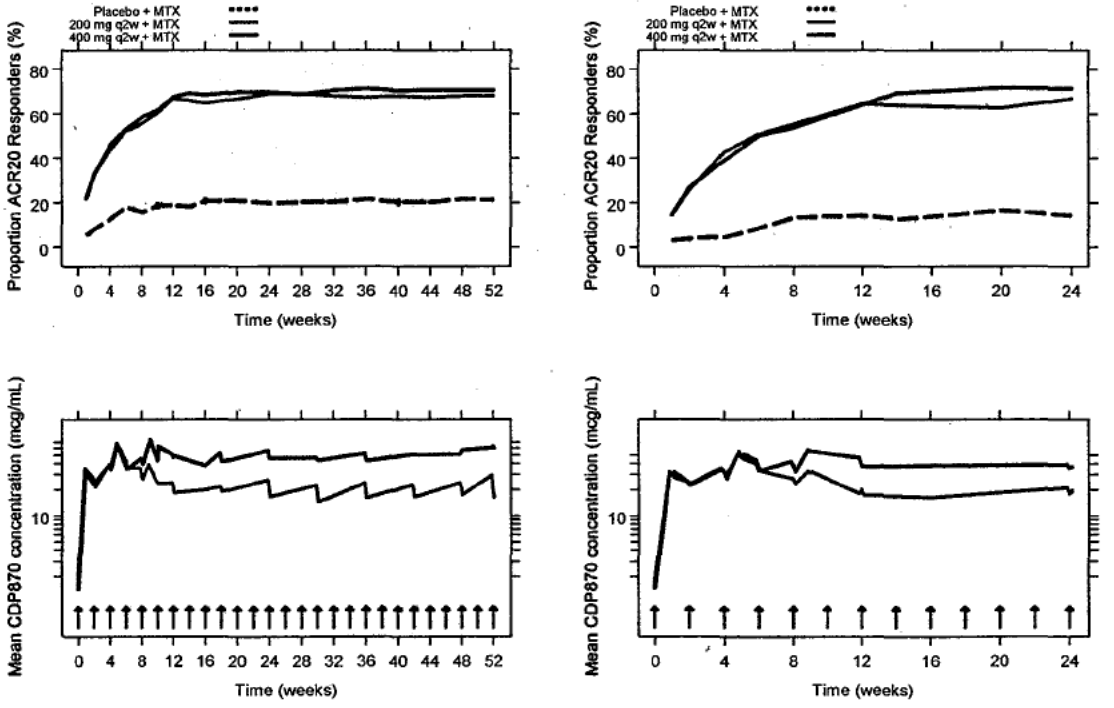


Figure Legend. Proportion ACR-20 responders (top) and mean CDP870 concentration

(bottom) time profiles for study 027 (left) and 050 (right). The ACR-20 response reaches steady-state around 12 weeks after initiation of treatment with the PK reaching levels above steady-state.

Predictions based on sponsor's PK/PD model showed that a loading dose would result in a typical 9% improvement in the probability of achieving an ACR 20 response rate at Week 12 following initiation of treatment compared with a non-loading dose regimen of 200 mg q2w. At Week 22, the predicted difference between the loading dose and the non-loading dose regimens was reduced to a 3% improvement in the probability of achieving an ACR 20 response. These predictions suggest that the main effectiveness benefit of the loading dose regimen is an improvement in speed of onset of ACR response predicted for the individual subject *(Source: Sponsor's report CDP870-079 page 95)*.

An exposure-response relationship at week 12 was identified similar to the one at the primary endpoint (see Figure below). The dosing regimen resulting in more than 90% of the patients attaining $C_{trough} > 5$ mcg/mL corresponding to the overall ACR-20 response rate of 60% at week 12 are 400 mg q2w + MTX at weeks 0, 2, and 4 followed by 200 mg q2w + MTX (orange line), 400 mg q2w + MTX (brown line) and 800 mg q4w (pink line).

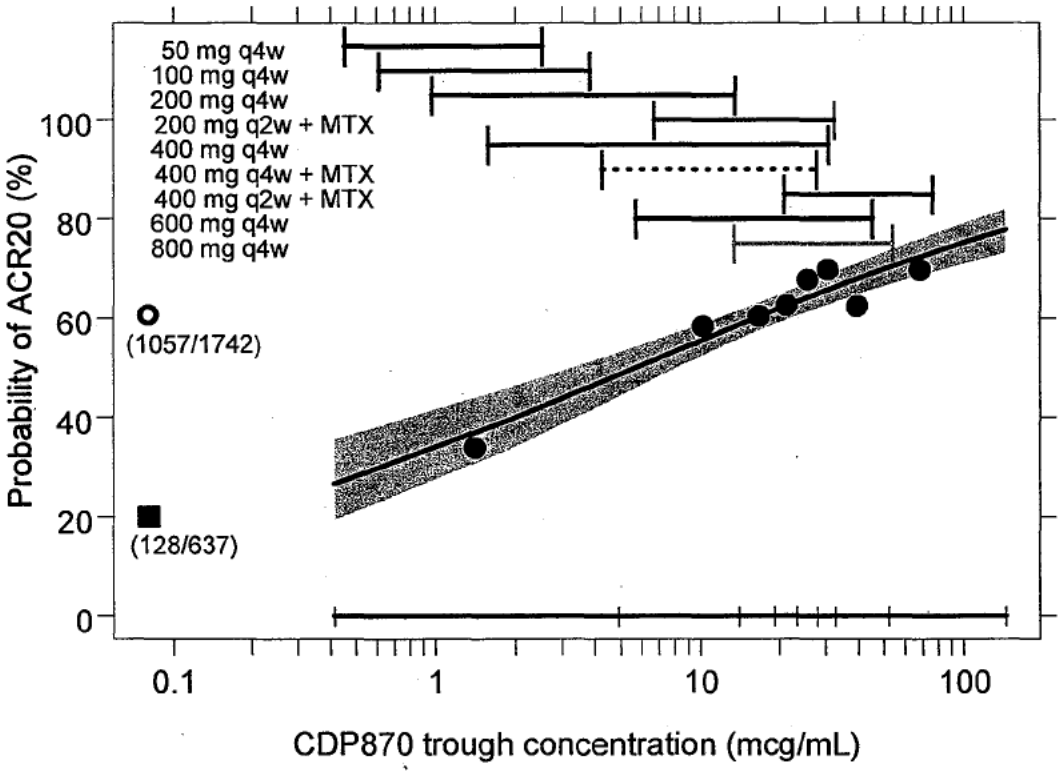


Figure Legend. Exposure-response relationship for effectiveness at week 12. Probability of ACR-20 response (LOCF) vs. CDP870 trough concentrations for studies 004, 011,

014, 027, 050 at week 12. The horizontal colored bars represent the 10-90th C_{trough} percentiles for the different dosing regimens.

Since a clear exposure-response relationship was identified for ACR-20 at week 12, it is desirable to get the CDP870 concentration levels faster to steady-state levels by administering a loading dose thereby increasing the probability of an earlier onset of action. Furthermore, the probability of developing antibodies was found to decrease with increasing concentrations and was also found to be irreversible thus supporting loading the subjects with higher doses to reduce the probability of developing antibodies.

Overall, an initial 400 mg loading dose at weeks 0, 2, and 4 is appropriate.

Is the maintenance infusion appropriate?

The sponsor is asking for approval of 200 mg q2w as well as 400 mg q4w. Based on the identified exposure-response relationship, splitting the 400 mg q4w dose to 200 mg q2w increases the 10th lowest C_{trough} percentile from 1 to 4 mcg/mL resulting in an increase from 50% to 70% in ACR-20 response. The proposed alternative maintenance dose of 400 mg q4w should therefore not be approved.

There does not seem to be a benefit in ACR-20 response on a population level by increasing the maintenance dose from 200 mg q2w to 400 mg q2w. However, on an individual level, patients with higher CDP870 clearance might benefit from the higher 400 mg q2w dose which increases the lowest 10th C_{trough} percentile from 4 to 10 mcg/mL.

A maintenance dose of 400 mg q2w also appears to be a valid option for patients not achieving ACR-20 response at e.g. week 12.

b) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

There is an increase in risk for infection in patients receiving Cimzia, as compared with patients receiving placebo. However, the risk of infection was not dose-related. In addition, there was no significant difference in the incidence of infections between the MTX and non-MTX RA patients.

The most frequent infections were those generally seen in the RA population, including upper respiratory tract infections, urinary tract infections, lower respiratory tract and lung infections, and herpes viral infections. In general, higher dose or dose frequency of Cimzia was not associated with an increased frequency of infections. No significant differences were observed between the 200 mg q2w and 400 mg q2w groups and the probability of infections.

Table: Percentage (number) of patients experiencing one or more infections and infestations and 4 high level terms.

	Placebo (N=647)	200 mg q2w + MTX (N=640)	400 mg q2w + MTX (N=635)	400 mg q4w (N=278)	All doses (N=1774)
Infections & Infestations	22.9% (148)	37.3% (239)	37.6% (239)	37.1% (103)	37.6% (667)

Upper respiratory tract infections	9.4% (74)	16.7% (107)	15.9% (101)	19.8% (55)	17.6% (313)
Urinary tract infections	4.5% (29)	6.3% (40)	7.2% (46)	2.2% (6)	5.8% (103)
Lower respiratory tract and lung infections	3.4% (22)	5.8% (37)	5.8% (37)	5.0% (14)	5.6% (100)
Herpes viral infections	1.2% (8)	3.1% (20)	4.1% (26)	3.6% (10)	3.6% (63)

Source : Table 8.1:10 in adverseevent.pdf on page 145-170

Exposure-safety relationships were identified for infections as well as high level terms such as upper and lower respiratory tract, urinary, and herpes viral infections in studies 004, 011, 014, 027, 050 using C_{max} concentrations as a measure of exposure (see Figure below). However, dose adjustments are not warranted since most infections were non-serious and easily resolved when treated.

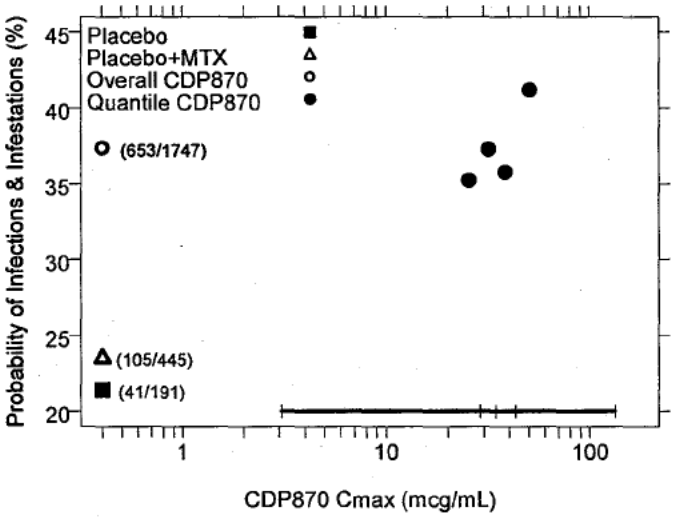
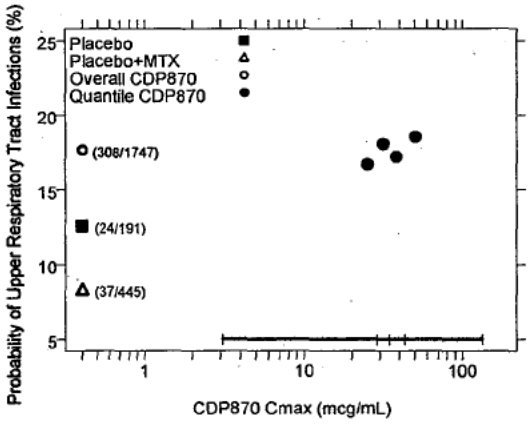
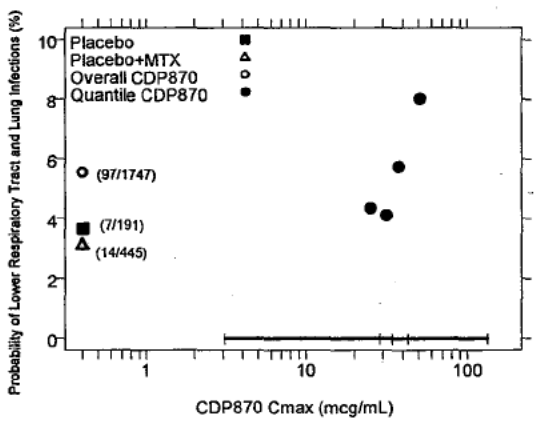


Figure Legend. Exposure-response relationship for infections vs. certolizumab C_{max} concentrations.





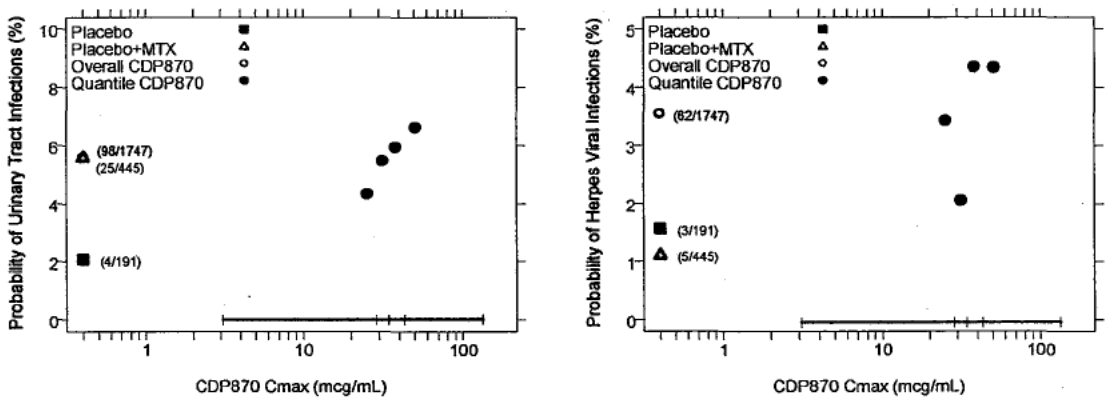


Figure Legend. Exposure-safety relationship for upper respiratory tract and lung (top left), lower respiratory tract (top right), urinary tract (lower left), and herpes viral (lower right) infections (non-serious and serious) vs. certolizumab C_{max} concentrations.

5. What are the PK characteristics of the drug and its major metabolite?

The table below lists various pharmacokinetic studies conducted in healthy volunteers and RA patients following intravenous and subcutaneous administration (see attached synopses).

Study #	Objective of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (# enrolled)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
CDP870-003	Bioavailability: sc vs. iv	Double-blind, double dummy; single ascending dose	20, 60 and 200 mg, sc or 1 mg/kg iv	30	Healthy Subjects	56 days
CDP870-038	Bioavailability: reconstituted lyophilized vs. liquid formulation	Randomized, parallel group, single dose, open label	Lyophilized and liquid; 400 mg; sc	48	Healthy Subjects	Single dose
CDP870-001	Tolerability & PK	Single iv infusion, ascending dose, dose placebo-controlled	0.3, 1, 3, or 10 mg/kg; iv	12 + 4 placebo	Healthy Subjects	3 months
CDP870-002	Tolerability & PK	Single iv infusion, ascending dose, placebo-controlled & open-label extension study	1, 5, and 20 mg/kg; iv	24 + 12 placebo 11 subjects (previously received placebo) 12 subjects (previously received CDP870)	RA Patients	8 weeks
PHA-024	Safety, tolerability, and PK in Japanese	Single sc, ascending dose, placebo-controlled	100, 400 and 800 mg; sc	36 + 12 placebo	Healthy Subjects (Japanese & Caucasian)	57 days
PHA-001	PK/interaction	Open-label, single-dose	400 mg; sc	16	RA Patients on MTX	57 days

a) What are the single dose and multiple dose PK parameters?

Pharmacokinetics of certolizumab are best described by a one compartment pharmacokinetic model with a first order absorption rate and a first order elimination rate.

Pharmacokinetics of certolizumab was investigated in healthy volunteers following intravenous (CDP-870-001) and subcutaneous (CDP870-003) administration. The pharmacokinetics of certolizumab appeared to be linear within the 0.3 – 10mg/kg range used in this study (See synopsis attached). Mean clearance (CL) values of 0.13 - 0.20 ml/hr/kg indicated that certolizumab is a low clearance drug with a mean terminal phase half-lives of 12.97 – 15.11 days. The volume of distribution was similar to total blood volume (60 – 102 ml/kg) and suggest that the majority of certolizumab in the body is restricted mainly to the blood.

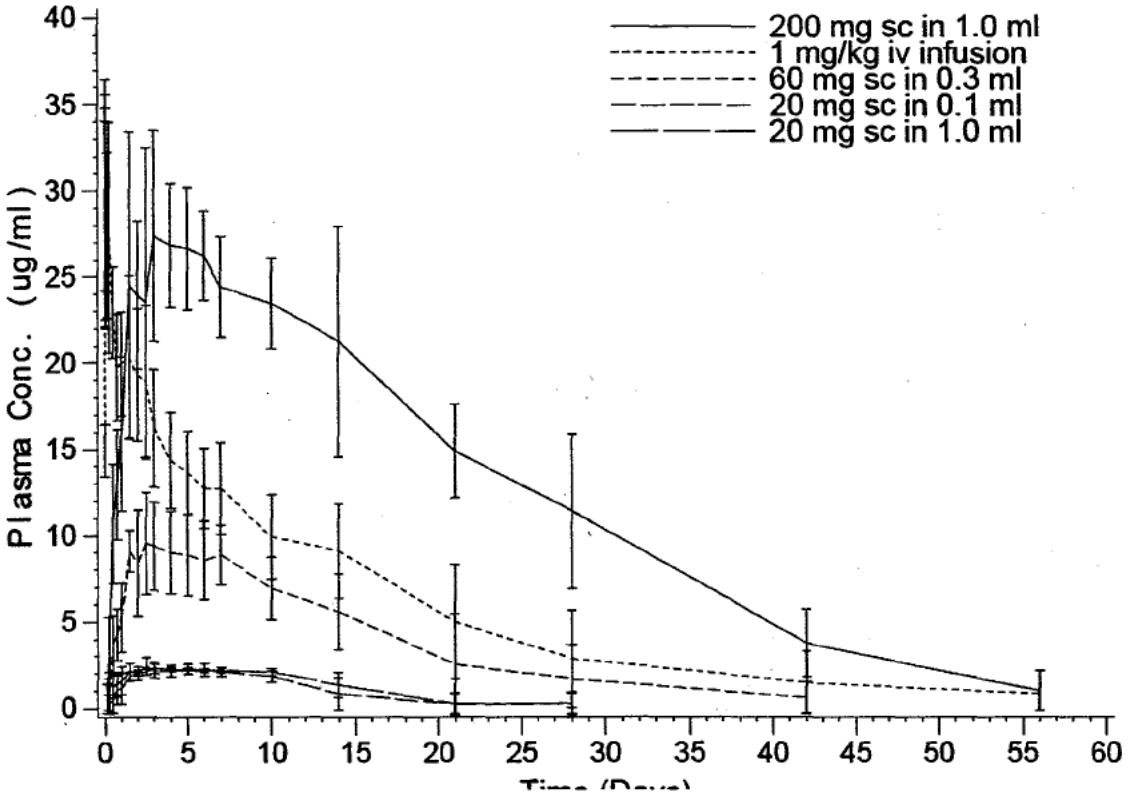


Figure Legend: Pharmacokinetic profile of certolizumab following IV and subcutaneous administration.

In study # CDP870-003 the pharmacokinetics of certolizumab following IV administration as a 60 minute constant rate infusion was compared to subcutaneous administration in limited number (n=6) of healthy male subjects (See synopsis attached). Peak plasma concentrations were noted in an average of 3.5 days (1.5 – 14 days). The bioavailability of certolizumab following sc administration of the certolizumab formulation was about 80% at 200 mg dose.

In study # 004, multiple dose PK of certolizumab was evaluated in the dose range of 50 – 800 mg following q4w administration for 12 weeks. The plasma concentrations (See table below) increase in a linear fashion in the evaluated dose range. Accumulation is not noted following repeated administration.

Table: Mean certolizumab concentrations (mcg/mL) at trough or 4 weeks after previous dose administration – First vs third dosing intervals in anti-certolizumab antibody positive and negative RA patients.

Treatment	Antibody Negative**		Antibody Positive ***	
	First Dosing Interval	Third Dosing Interval	First Dosing Interval	Third Dosing Interval
CDP-870 50 mg	2.1	1.4 *	1.9	1.1 *
CDP-870 100 mg	4.8	2.0 *	4.0	1.5 *
CDP-870 200 mg	10.0	7.2 *	7.1	1.6 *
CDP-870 400 mg	16.2	15.0	12.2	3.5 *
CDP-870 600 mg	23.8	24.3	9.1	4.3
CDP-870 800 mg	29.2	31.7	19.3	2.4

* $p < 0.05$ versus the antibody negative value (two-sample t-test).
** Anti-CDP-870 antibody plasma level ≤2.4 mcg/mL
*** Anti-CDP-870 antibody plasma level >2.4 mcg/mL.

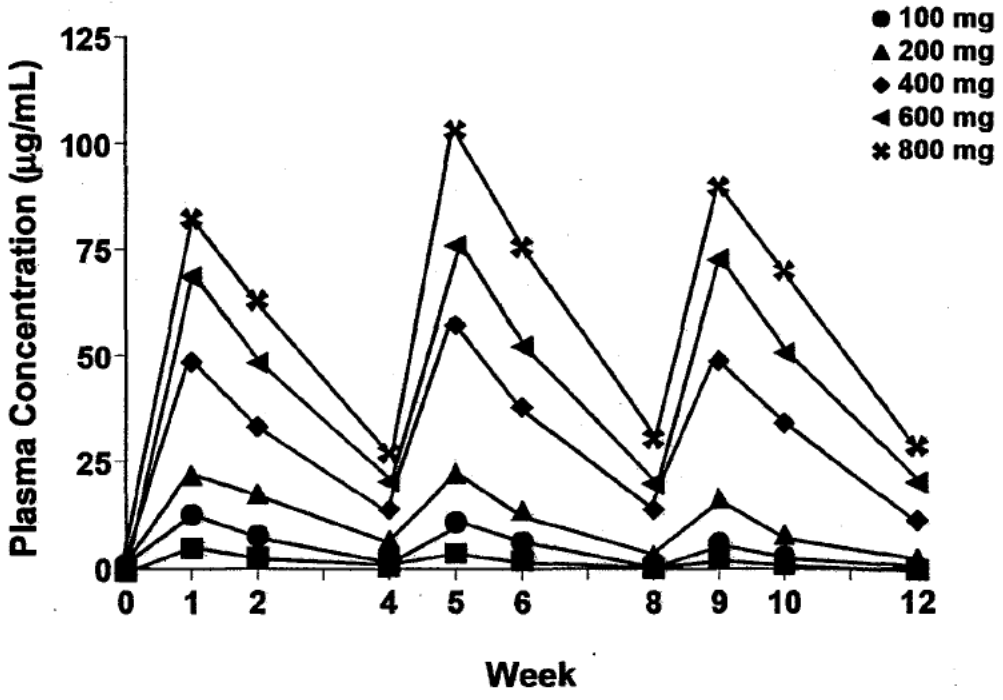


Figure Legend: Mean observed plasma certolizumab concentrations in study # 004.

In study # CDP87O-002, RA patients received a single intravenous infusion over 60 minutes of 1, 5 or 20 mg/kg certolizumab or placebo. Patients who completed the eight week follow-up period had the opportunity to receive a second dose of the same treatment. Certolizumab plasma concentrations in these patients are shown below.

TREATMENT		PRE-INFUSION	END OF INFUSION	TIME SINCE THE START OF INFUSION				
				1 WEEK	2 WEEKS	4 WEEKS	6 WEEKS	8 WEEKS
1 mg/kg CDP870	MEAN	1.054	27.778	11.104	7.277	3.427	1.828	1.307
	95% CI	0.714, 1.558	23.217, 33.236	8.783, 14.040	5.983, 8.852	2.665, 4.406	1.551, 2.154	1.017, 1.680
	N	8	8	8	8	8	8	7
5 mg/kg CDP870	MEAN	0.569	109.265	45.143	29.836	12.962	5.021	2.220
	95% CI	0.468, 0.692	81.198, 147.035	40.668, 50.110	23.422, 35.995	8.318, 20.011	2.914, 8.651	1.006, 4.898
	N	8	8	8	8	8	8	8
20 mg/kg CDP870	MEAN	0.569	467.653	180.432	104.061	42.593	22.423	9.177
	95% CI	0.613, 0.783	402.332, 543.580	149.924, 217.147	82.560, 131.160	29.189, 62.152	14.691, 34.226	6.096, 13.817
	N	8	6	8	8	7	8	8

Note: The geometric mean and its associated 95% confidence interval are presented.
Values below the limit of quantification of 0.41 µg/mL were set to the limit of quantification.

b) What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The inter- and intra-subject variability of certolizumab PK parameters are listed below. As described in the intrinsic factors section below bodyweight and antibody response are the major causes of variability in PK.

The population PK parameter estimates for certolizumab using data from studies # 001, 004, 011, 014, 027 and 050 are tabulated below. The inter-subject variability in parameter estimates is also presented below.

Parameter	Estimate [95% CI]	Precision (%CV)
Absorption rate constant with solution formulation	0.811 [0.788 – 0.834]	1.47
Absorption rate constant (ka)	0.419 [0.366 – 0.472]	6.42
Clearance in antibody negative patients	0.505 [0.493 – 0.517]	1.20
Clearance in antibody negative patients	2.91 [2.64 – 3.18]	4.78
Clearance/BW	0.600 [0.525 – 0.675]	6.40
Volume of distribution	8.01 [7.77 – 8.25]	1.52
Variability	**Estimate (%CV)**	**Precision (%CV)**
Inter-subject variability in ka	39.1	27.2
Inter-subject variability in D1	55.9	29.2
Inter-subject variability in CL/F	30.8	5.03
Inter-occasion variability in CL/F	22.0	11.3
Inter-subject variability in V/F	30.9	8.89
Covariance between CL and V	22.1	10.5
Residual variability in concentration	29.7	7.50

2.3 Intrinsic Factors

Only bodyweight and anti-certolizumab antibody formation significantly influenced PK of certolizumab.

Effect of race, age, gender, and bodyweight and anti-certolizumab antibody response was evaluated on PK and ACR20 response of certolizumab. Clinical studies included limited

number of geriatric subjects to allow analysis of effect of age on PK of certolizumab. However, pediatric patients & pregnant and lactating women were not included in the clinical studies. Certolizumab pegol does not cross-react with mouse or rat TNFα, reproduction studies were performed in rats using a rodent anti-**murine TNFα** pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol. It is not known whether certolizumab is excreted in human milk. Study#PHA-024 evaluated PK of certolizumab following single 100, 400 and 800 mg SC dose administration in Caucasian and Japanese subjects. Plasma certolizumab levels were similar between the two groups (see attached synopsis for study PHA-024).

1. **Is the fixed dose regimen appropriate considering the effect of body weight on certolizumab PK?**

Fixed dosing, i.e. not body weight corrected dosing, is appropriate since the probability of ACR-20 response is similar (~70%) across all body weight quartiles for antibody negative patients as illustrated in Figure below (right) due to the shallow body weight – C_{trough} relationship and high enough exposures at the proposed dosing regimen.

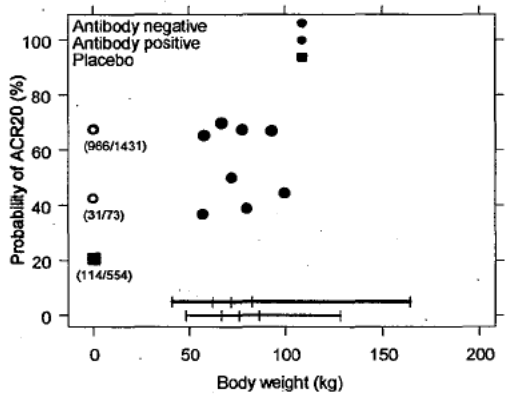


Figure Legend. (Left) Steady-state certolizumab trough concentration vs. body weight for patients receiving 200 mg q2w in studies 027 and 050. The black dots and red crosses symbolize antibody negative and positive patients, respectively. **(Right)** Probability of ACR-20 response at week 24 for studies 027 and 050 vs. body weight. The red dots represent the median body weight in each quartile and the associated observed ACR-20 (LOCF) response rate.

In addition, body weight and antibody status were identified as covariates for clearance in sponsor's population PK analysis with the latter being the major contributor to variability in clearance (see Figures below).

Figure Legend. (Left) Clearance vs. body weight for antibody negative (black circles) and positive (red crosses) patients with population predictions (red lines). **(Right)** Box plot of individual predicted clearances for antibody negative and positive patients together with population predictions (red lines).

The presence of antibodies has a significant effect on the PK of certolizumab. The population PK analysis showed that antibodies increased the clearance of certolizumab by 3-fold. The increase in certolizumab clearance caused by antibodies results in a 46 % reduction in C_{max}, 82 % reduction in C_{trough}, and 60 % reduction in AUC for the dose interval. Body weight was found to have an effect of ±20% on C_{max}, ±50% on C_{trough}, and ±30% on AUC.

2. What are the characteristics and extent of anti-certolizumab antibody formation; and what is the impact of anti-certolizumab antibody formation on the pharmacokinetics, pharmacodynamics or clinical response of certolizumab?

Significant number of RA patients developed anti-certolizumab antibodies with continued treatment with certolizumab. Certolizumab dose-related decrease in anti-certolizumab antibodies was noted. Concomitant administration with methotrexate decreased the incidence of antibodies.

In RA patients positive for anti-certolizumab antibodies increase in systemic clearance of certolizumab and decrease in its pharmacodynamic effects and clinical response (ACR20) is noted.

Dose-related decrease in anti-certolizumab antibody formation

In the dose-ranging study #004 where RA patients received 50 – 800 mg q4W doses of certolizumab without methotrexate, plasma samples were analyzed for anti-certolizumab antibodies every four weeks starting at screening. Formation of anti-certolizumab antibodies was noted as early as 8 weeks after treatment initiation and peaks after 12-16

weeks. It appears that the antibody formation is inversely proportional to the certolizumab dose as illustrated in Table below.

Table Legend. Percentage antibody positive patients at week 12 across dose groups in dose-ranging study 004 administered q4w

	50 mg - MTX (N=40)	100 mg - MTX (N=40)	200 mg - MTX (N=41)	400 mg - MTX (N=43)	600 mg - MTX (N=39)	800 mg - MTX (N=39)
% Antibody positive patients	**56**	**56**	**58**	**20**	**11**	**5**

Upon completion of the double-blind treatment phase at week 16, RA patients receiving 50, 100, 200 and 400 mg (or Panel 1) in the double-blind phase received 200 mg q4w initially followed by 400 mg q4w SC. The patients in 600 and 800 mg groups (panel 2) received 400 mg SC q4w only. The incidence of antibodies to CDP-870 appears to increase following cessation of treatment which may represent increased assay accuracy due to decreased interference from circulating concentrations of CDP-870.

Effect of methotrexate on anti-certolizumab antibody formation

Methotrexate administration seems to have significant negative impact on anti-certolizumab formation.

Across studies the percentage of RA patients turning anti-certolizumab antibody positive is lower with methotrexate treatment (5% in study # 014) as against patients not receiving methotrexate (20% in study # 011).

Table Legend. Overall antibody status at some point in the study across dose groups in phase III studies 011, 014, 027, and 050 *(Source: Sponsor's immunogenicity report 400001600 p. 32-36).*

	400 mg q4w - MTX (N=124) Study # 011	400 mg q4w + MTX (N=124) Study #014	200 mg q2w + MTX (N=640) Studies 027 & 050	400 mg q2w + MTX (N=633) Studies 027 & 050
% Antibody positive patients	**20**	**5**	**10**	**2**

Since 200 mg q2w regimen was not evaluated without methotrexate, data is not available on % of RA patients positive for anti-certolizumab antibodies. However, judging by the dose-response and effect of methotrexate on the antibody formation, the 200 mg q2w regimen may be similar to the 400 mg q4w regimen without methotrexate.

Impact of anti-certolizumab antibodies on certolizumab pharmacokinetics

A 3-fold increase in certolizumab clearance is seen for antibody positive patients reducing the certolizumab trough concentrations below 10 mcg/mL for the majority of antibody positive patients in studies 014, 027, and 050 utilizing background MTX.

Figure Legend: Box plot of individual predicted clearances for antibody negative and positive patients together with population predictions (red lines).

The probability of developing antibodies is clearly increased in study 011 (without MTX) compared to study 014 (with MTX) where the only difference between the two studies is the concomitant administration of MTX in study 014. In antibody positive patients, the ACR-20 response rate is reduced to around 40% (see Figure below right).

Figure Legend. Certolizumab concentration-time profiles in studies 011, 014, 027, and 050. The black dots and red crosses symbolize antibody negative and positive patients, respectively.

The probability of developing antibodies decreases with increasing certolizumab steady-state trough concentrations, i.e. the lower the certolizumab steady-state trough concentration, the higher the probability of having anti-certolizumab antibodies (see Figure below). Patients with certolizumab steady-state trough concentrations above 10 mcg/mL were found to have very little probability of developing antibody. This observation may be due to interference from circulating concentrations of certolizumab.

Only 400 mg q2w + MTX and 800 mg q4w dosing regimens result in 90% of patients having trough concentrations above 10 mcg/mL and thus very little antibody formation (see horizontal colored bars in Figure below).

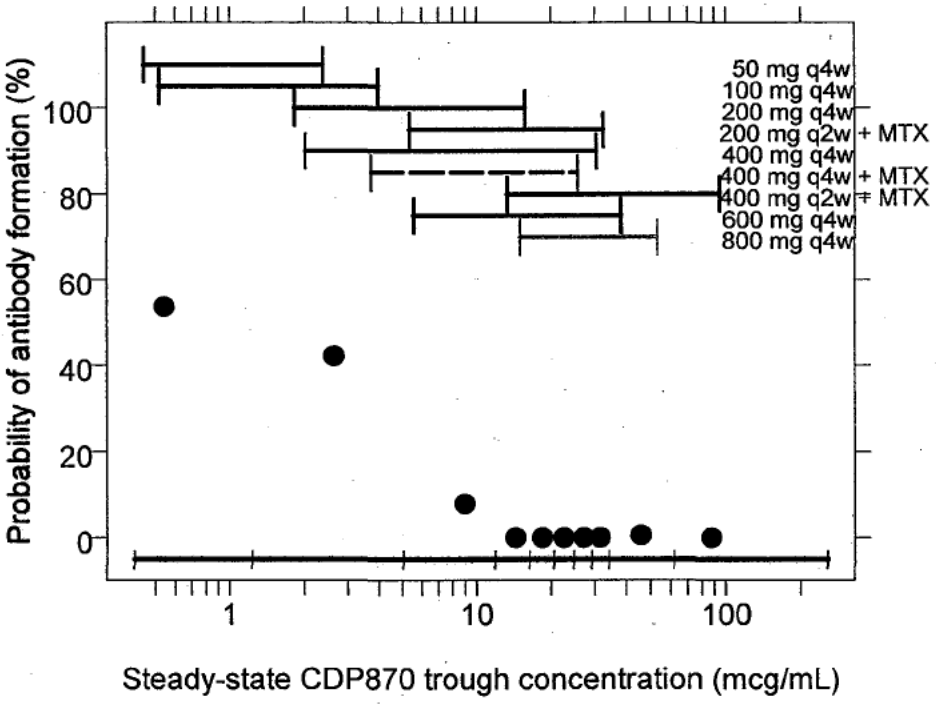


Figure Legend. Probability of antibody formation vs. steady-state certolizumab trough concentration ($C_{ss,trough}$) from studies 004, 011, 014, 027, and 050. The horizontal colored bars represent the 10-90th $C_{ss,trough}$ percentiles for the different dosing regimens.

Impact of anti-certolizumab antibodies on certolizumab clinical response & pharmacodynamics

Compared to anti-certolizumab antibody negative RA patients, antibody positive patients produced a lower ACR 20 response and change in C-reactive protein levels, which is also a component of the ACR20 criteria and a well accepted pharmacodynamic response.

Studies #027 and #050:

As described above, Studies #027 and #050 evaluated efficacy of certolizumab in RA patients on stable doses of methotrexate. Among 393 RA patients receiving 200 mg q2w regimen 10.8% were antibody positive. These patients had lower ACR20 response (50 % response) compared to antibody negative patients (60% response). Subgroup analysis testing ACR20 results against antibody status of the RA patient revealed that % ACR20 responders was lower decreased was reduced in the antibody positive patients (See tables below).

Table: Comparison of the ACR20 Response by Antibody Status at Week 24 – ITT Population (Study CDP870-027)

Week 24	**Certolizumab 200 mg + MTX (N = 393)**		**Certolizumab 400 mg + MTX (N = 390)**	
	Ab+	Ab-	Ab+	Ab-
n (%)	42 (10.8%)	346 (89.2%)	8 (2.1%)	380 (97.9%)
Responder	20 (47.6%)	208 (60.1%)	4 (50%)	232 (61.1%)
Non-Responder	22 (52.4%)	138 (39.9%)	4 (50%)	148 (38.9%)
Treatment by subgroup interaction(a) , p value = 0.978				

(a) Wald p-values for the comparison of the treatment groups were calculated using logistic regression with factors for treatment, subgroup, region, and subgroup by treatment interaction. Note: Patients who withdrew for any reason or used rescue medication were considered as non-responders from that time-point onwards.

Table: Comparison of the ACR-20 Responder Rate by Antibody Status at Week 24 – ITT Population (Study CDP870-050)

Week 24	**Certolizumab 200 mg + MTX (N = 246)**		**Certolizumab 400 mg + MTX (N = 246)**	
	Ab+	Ab-	Ab+	Ab-
n (%)	20 (8.1%)	226 (91.9%)	4 (1.6%)	241 (98.0%)
Responder	7 (35.0%)	134 (59.3%)	2 (50.0%)	139 (57.7%)
Non-Responder	13 (65.0%)	92 (40.7%)	2 (50.0%)	102 (42.3%)
Treatment by subgroup interaction(a) , p=0.854				

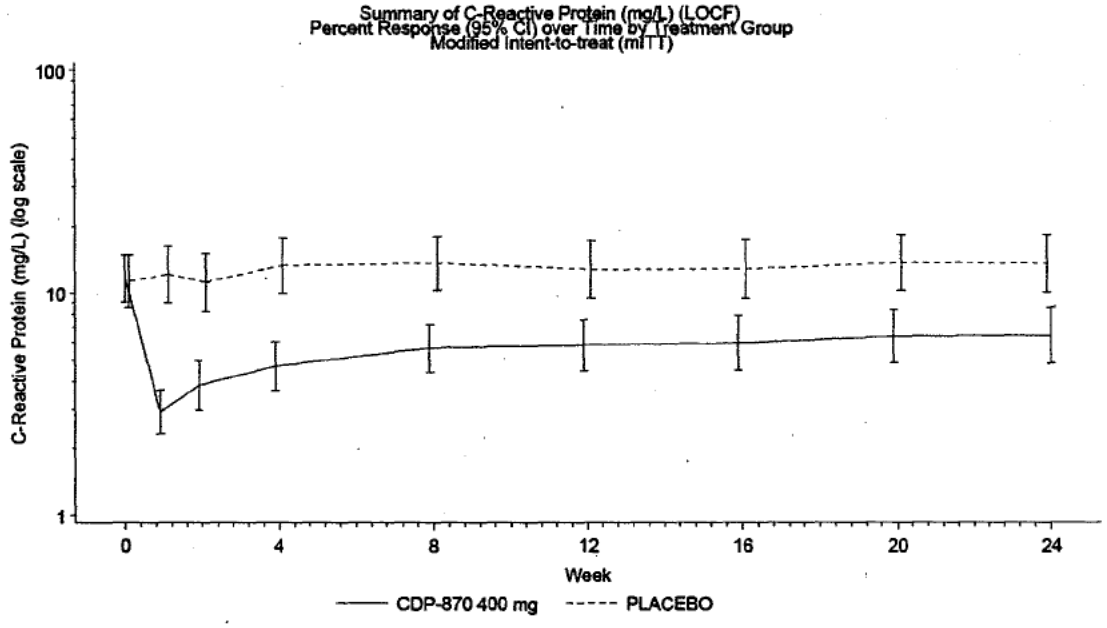
(a) Wald p-values for the comparison of the treatment groups were calculated using logistic regression with factors for treatment, subgroup, region, and subgroup by treatment interaction. Note: Patients who withdrew for any reason or used rescue medication were considered as non-responders from that time-point onwards.

Study # 011

Twenty percent of RA patients receiving 400 mg q4w certolizumab developed antibodies by week 12 in **Study # 011**. However, the ACR20 response was highly variable and hence not very different between antibody positive and negative patients. The decrease in ACR20 responder status after week 16 is due to drop outs from the study. Accordingly, the certolizumab treatment group showed persistent high ACR20 response over time compared to placebo irrespective of antibody status.

C-reactive protein (CRP) levels, indicator of inflammation, were measured as a pharmacodynamic endpoint and as a clinical response indicator in most clinical studies. Significant decrease in CRP levels was noted immediately after treatment initiation with

certolizumab compared to placebo (see figure below).



While in RA patients treated with certolizumab CRP levels increased upon development of antibodies by weeks 4 and later, CRP levels remained low in antibody negative patients.

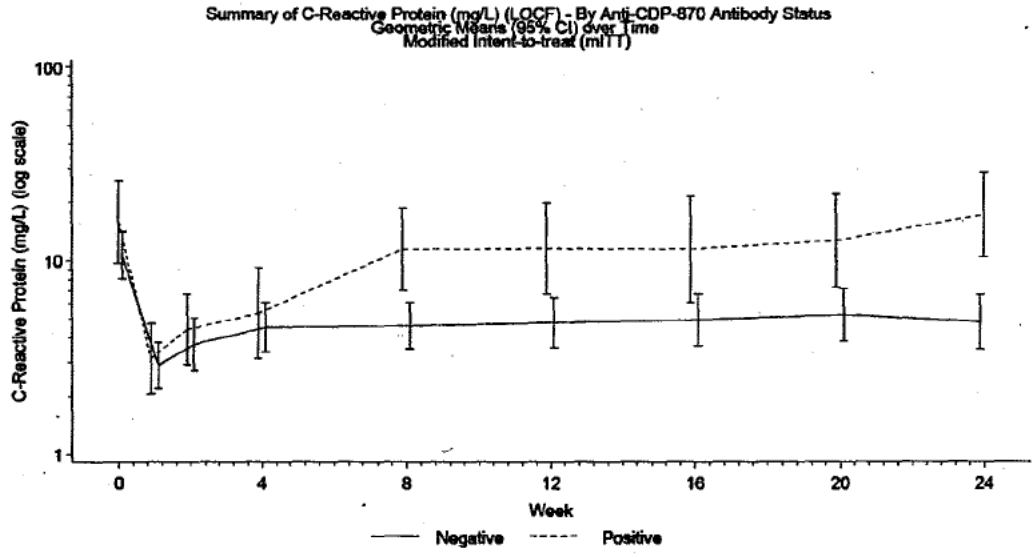


Table: C-reactive protein (CRP) (mg/L) by Anti-CDP-870 Antibody Status in all RA patients randomized to certolizumab in Study # 011.

	Antibody Negative	Antibody Positive	
	Anti-CDP-870 antibody level <= 2.4 units/mL (a)	Anti-CDP-870 antibody level > 2.4 units/mL (a)	P-value(b)
Baseline	(N=86)	(N=25)	

Geometric mean	10.65	15.73	
95% confidence interval	(8.01,14.15)	(9.67,25.56)	
Week 24			
Geometric mean	4.83	17.22	
95% confidence interval	(3.50, 6.67)	(10.44,28.43)	
Change from Baseline			
Geometric mean	0.45	1.10	0.002 **
95% confidence interval	(0.35, 0.59)	(0.70, 1.73)	

(a) Based on maximum antibody level during 24 week treatment period
(b) From Analysis of Variance model using log-transformed CRP values

In study # 014, where 400 mgq4w with methotrexate was evaluated, too few patients developed anti-certolizumab antibodies to allow any meaningful analysis of the ACR-20 response, CRP level changes by antibody status.

Study #004

In the dose ranging study #004, CRP levels were assessed at baseline and up to 12 weeks during the double-blind phase. Observed means, mean change from Baseline and statistical tests for change from Baseline for plasma CRP, ITT cohort, Panel 1 and Panel 2, respectively are presented in the table below. A significant decrease in CRP levels is noted immediately after initiated treatment with certolizumab. When considering the RA patients with out regard to their antibody status, this early pharmacodynamic response was not maintained and none of the certolizumab treatment groups was distinguishable from placebo at Week 12 (see table below).

Table: Mean Change from Baseline in CRP (mg/L): Panel 1

	Placebo	50 mg SC	100 mg SC	200 mg SC	400 mg SC
N	40	39	40	41	42
Week 0	29.9	26.4	33.1	40.8	23.8
Least Squares Mean Change					
Week 1	4.6	-18.3***	-22.3***	-19.3***	-20.6***
Week 2	5.4	-13.9***	-19.3***	-19.3***	-20.7***
Week 4	2.0	-4.7	-15.6***	-17.9***	-17.5***
Week 8	1.3	4.4	-6.8	-3.8	-10.3*
Week 12	1.7	5.3	-2.5	-0.8	-6.8

Table: Mean Change from Baseline in CRP (mg/L): Panel 2

	Placebo	600 mg SC	800 mg SC
N	43	39	38
Week 0	36.8	33.3	33.5
Least Squares Mean Change			
Week 1	4.9	-19.3***	-25.6***
Week 2	2.3	-18.6***	-19.0***
Week 4	-4.0	-16.6**	-18.8***
Week 8	1.4	-16.5***	-21.1***
Week 12	0.2	-18.8***	-20.4***

However, as shown in the table below, at week 12 of treatment CRP levels were higher in antibody positive patients compared to antibody negative RA patients. This observation possibly explains the noted loss in pharmacodynamic response initially noted.

	CDP-870 mg SC Every 4 Weeks					
	50 mg	100 mg	200 mg	400 mg	600 mg	800 mg
N	39	40	41	42	39	38
Antibody Negative*, Mean (SD)	26.9 (36.3)	17.4 (22.9)	22.9 (32.2)	15.7 (30.8)	17.6 (24.5)	13.9 (20.8)
Antibody Positive**, Mean (SD)	36.6 (37.7)	39 (39.9)	47 (47.4)	35 (47.2)	12 (10.6)	46.3 (56.4)

* Maximum anti-CDP-870 antibody plasma level ≤2.4 mcg/mL.
** Maximum anti-CDP-870 antibody plasma level ≥2.4 mcg/mL.

Since it is not feasible to measure patient's antibody status in a clinical setting, and the fact that antibody formation does not appear to be reversible with increased certolizumab dosing (study #004 open label period), a fixed dosing regimen as investigated and shown to be efficacious is adequate.

2.4 Extrinsic Factors

1) Are other medications expected for use with certolizumab? If so, are any drug interactions anticipated that would warrant dosage adjustment?

Medications such as methotrexate, glucocorticoids, DMARDs and NSAIDs are anticipated for concomitant administration with certolizumab. Certolizumab may be administered with or without methotrexate. Dosage adjustment is not necessary with respect to these medications.

Formal drug-drug interaction studies have not been conducted with certolizumab in RA patients. Based on data from clinical studies, population pharmacokinetic analysis evaluated the effect of concomitant drug treatment with methotrexate, corticosteroids, nonsteroidal anti-inflammatory drugs, analgesics or immunosupressants on the pharmacokinetics of certolizumab pegol in patients with rheumatoid arthritis. However, population analysis can only be used to provide further evidence of the absence of a drug-drug interaction when this is supported by prior evidence and mechanistic data. It is unlikely that population analysis can be used to prove the absence of an interaction that is strongly suggested by information arising from in vivo studies specifically designed to assess a drug-drug interaction.

Certolizumab clinical response in presence of methotrexate

When looking at the primary endpoint (ACR-20 response at week 24) and the mean certolizumab concentration-time profile, MTX does not appear to have any major impact for certolizumab treated patients whereas there is a 5% increase in response rate for patients treated with placebo + MTX compared to placebo alone.

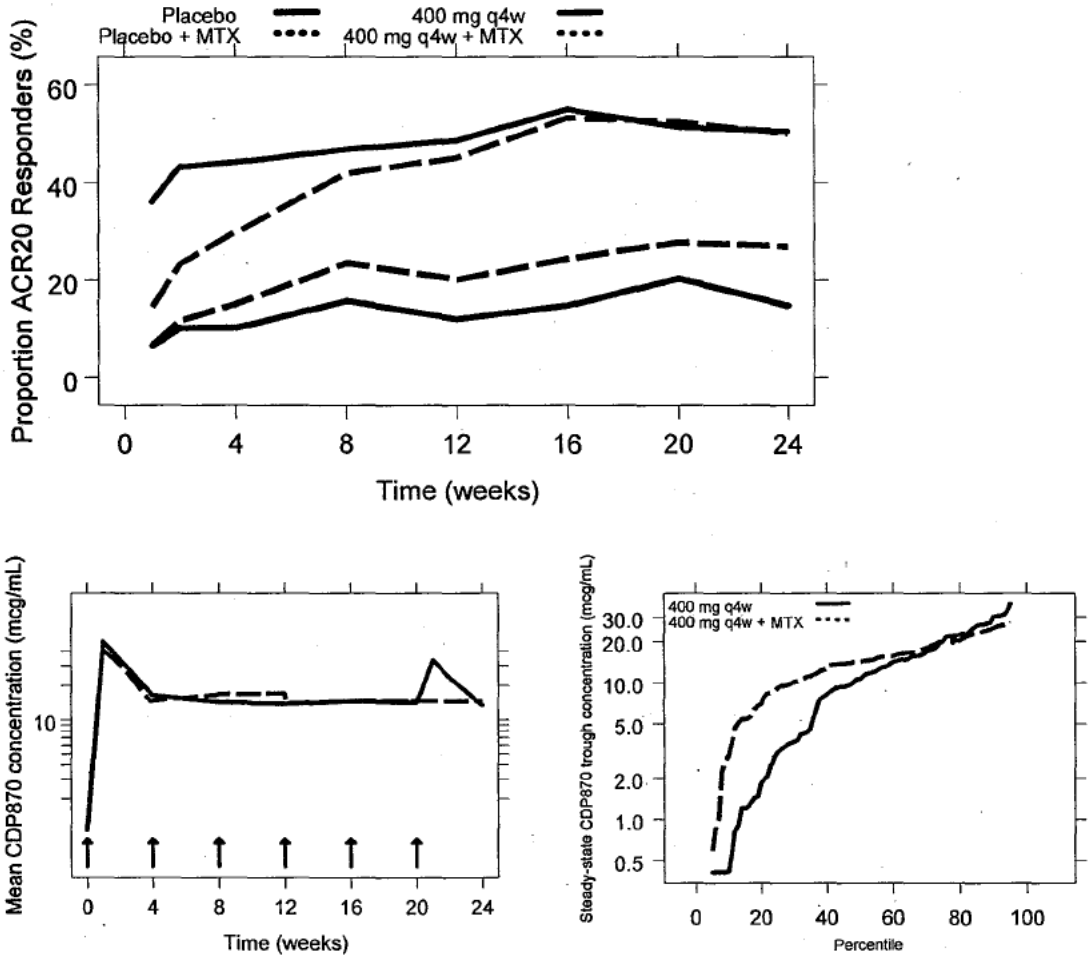


Figure Legend. Proportion ACR-20 responders over time (top), mean certolizumab concentration-time profile (bottom left), and distribution of C_{trough} **for studies 011 and 014** utilizing 400 mg q4w with (dashed lines) and without concomitant (solid lines) methotrexate (MTX), respectively.

However, there is an indirect benefit of concomitant MTX on the ACR-20 response rate by reducing the probability of antibody formation which results in higher steady-state certolizumab trough concentrations (see figures above) and thereby higher probability of ACR-20 response (see figure above). Due to the relative low incidence of antibodies at 400 mg q4w, the indirect effect of concomitant MTX on ACR-20 is low.

Coadministration of certolizumab with methotrexate did not have a clinically significant effect on the pharmacokinetic profile of methotrexate (See attached synopsis for study PHA-001). Effect of methotrexate on anti-certolizumab antibody formation is discussed in detail under Intrinsic Factors section above. Clinical studies did not evaluate the effect of introducing methotrexate on antibody response in RA patients positive for anti-certolizumab antibodies.

Certolizumab clinical response in presence of analgesics

Patients with concomitant administration of analgesics were found to have lower ACR-20 response rates of 55% compared to 68% without analgesics. This identified difference in response rates was not found to be due to differences in exposure (see Figure below on the left). US patients had 10% lower ACR-20 response rates compared to non-US patients (see Figure below on the right). A similar finding was observed in the Crohn's Disease studies.

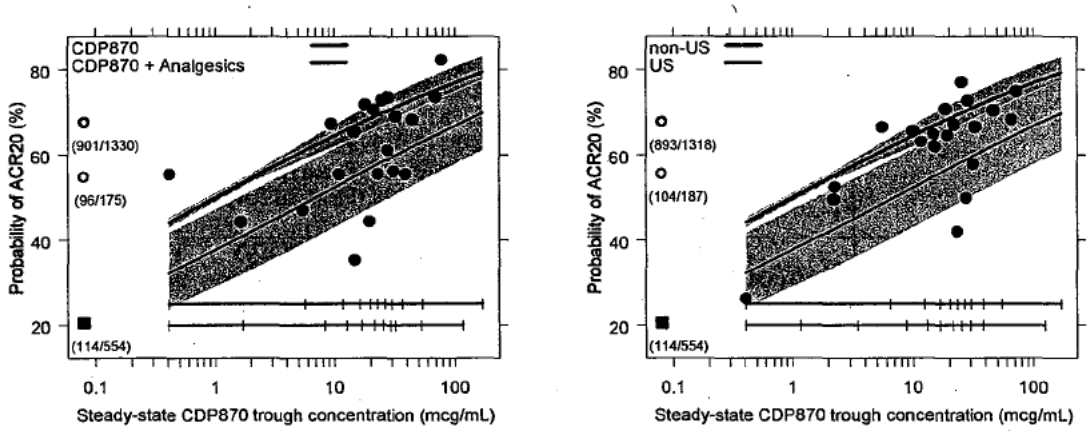


Figure Legend: Exposure-response for **(left)** concomitant administration of analgesics and **(right)** geographical region (right). Probability of ACR-20 response vs. steady-state certolizumab trough concentrations ($C_{ss,trough}$) at week 24 for studies 011, 014, 027, and 050. The overall certolizumab treated without concomitant analgesics/non-US (open red circle) and with concomitant analgesics/US (open blue circle), and placebo (solid black square) response rates are shown at the left hand side of the figure. **The solid red and blue** lines are the predicted ACR-20 response rate from the lowest to highest observed $C_{ss,trough}$ and the associated 95% CI (shaded area) for certolizumab treated with/without concomitant analgesics and US/non-US, **respectively. The red and blue dots represent the** median $C_{ss,trough}$ in each decatile and the associated observed ACR-20 (LOCF) response rate.

2.5 General Biopharmaceutics

2.5.1 Are the various formulations of certolizumab used throughout the clinical development adequately linked?

The table below indicates the various formulations used in the clinical studies:

Drug Product Pharmaceutical Form/Presentation Clinical Trial Phase No.	Formulation and Strength	Used in Clinical Studies
Liquid formulation Phase I/II	(b) (4)	CDP870-001 (Phase I HV) CDP870-003 (Phase I HV) CDP870-002 (Phase II RA)
Liquid formulation Phase I/II		PHA-001 (Phase II RA) CDP870-003 (Phase I HV) CDP870-004 (Phase II RA)
Lyophilized Phase I/III	After reconstitution: 200 mg/mL 0.9 mg/mL lactic acid, 100 mg/mL sucrose 0.1 mg/mL P20 pH 5.2	PHA-024 (Phase I HV) CDP870-038 (Phase I HV) CDP870-011 (Phase III RA) CDP870-014 (Phase III RA) CDP870-015 (Phase III RA) CDP870-027 (Phase III RA) CDP870-028 (Phase III RA)
Liquid formulation Phase III	200 mg/mL 10 mM acetate / 125mM sodium chloride pH4.7	CDP870-038 (Phase I HV) CDP870-050 (Phase III RA) CDP870-051 (Phase III RA)

The pharmacokinetics of certolizumab was investigated in healthy subjects (Study # CDP870-038) following subcutaneous administration to compare two different formulations of CIMZIA (lyophilized powder for reconstitution vs prefilled syringes with solution). Twenty four healthy adult male subjects were enrolled in this study per each of the two treatment groups (see attached synopsis). All completed the study and were evaluable for pharmacokinetic and statistical analyses. The mean concentration vs time plots (see figure below) and the pharmacokinetic parameters (see table below) of two certolizumab pegol formulations showed slightly lower Cmax and AUC in the test formulation compared to the reference formulation (AUC(0-t), AUC and Cmax were 13%, 5% and 9% lower in the test formulation).

Parameters	Certolizumab pegol 400 mg Lyophilized formulation [(a)]	Certolizumab pegol 400 mg Solution formulation[(a)]	CV[(b)] (%)	Test versus Reference[(c)]	
				Point estimate	90% CI
Cmax (µg/mL)	63.48 (54.74-73.61)	57.99 (50.00-67.24)	36.0	91.35	(76.71-108.8)
AUC(0-t) (µg.d/mL)	1355 (1184-1551)	1178 (1029-1349)	32.9	86.97	(74.15-102.0)
AUC (µg.d/mL)	1392 (1218-1592)	1209 (1057-1382)	32.6	86.82	(74.13-101.7)
tmax [(d)]	5.50 (3.00-21.00)	5.00 (3.00-14.00)	NA	-0.001	(-1.000-0.000)

(a) Values are geometric least square means (95% confidence interval), tmax values are median (minimum-maximum)
(b) Inter-subject coefficient of variation (%) (c) Point estimate (90% confidence interval) for the test/reference geometric least square means ratio derived from ANOVA; (d) for tmax: median point estimate (90% non-parametric confidence interval) of the difference test-reference

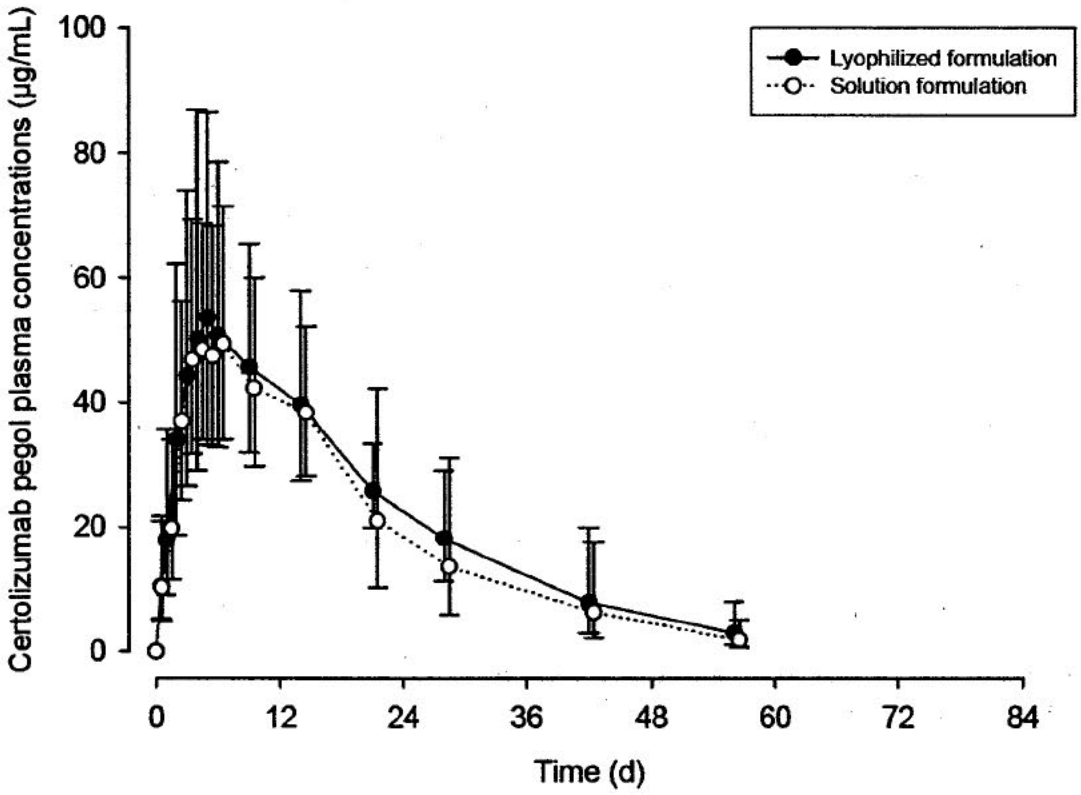


Figure Legend: PK profile of certolizumab following administration of lyophilized formulation and solution formulation.

Although the difference was not statistically significant between the two formulations regarding Cmax, AUC(0-t) and AUC, the lower limit of the 90% CI of the test/reference ratio was lower than the lower bound on 80%-125% limit of bioequivalence. Population PK analysis also confirmed that the lyophilized powder formulation employed in studies # 011 and 014 yielded slightly higher steady-state trough levels compared to solution formulation used in clinical efficacy study # 050.

Despite the observed PK difference, the solution formulation employed in Study # 050 resulted in successful accomplishment of primary efficacy endpoint at 200mg q2w and 400mg q2w doses compared to placebo (see discussion on exposure-response in QBR section 2.2 (4)).

2.6 Analytical

A validated sandwich enzyme-linked immunosorbent assay (ELISA) method was used to determine the concentration of certolizumab in human plasma collected from various clinical studies (see validation report attached).

4 Appendix

4.1 Pharmacometrics review by Dr. Christoffer Tornoe (see attached)

APPEARS THIS WAY ON ORIGINAL

4 Appendix

4.1 Pharmacometrics review by Dr. Christoffer Tornoe (see attached)

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PHARMACOMETRICS REVIEW

BLA:	125271
Drug name:	Cimzia (Certolizumab pegol)
Indication:	RA
Proposed Regimen (Sponsor):	400 mg q2w+MTX at weeks 0, 2 and 4 followed by 200 mg q2w+MTX or 400 mg q4w
Applicant:	UCB
Clinical Pharmacology Reviewer	Srikanth Nallani, Ph.D.
Clinical Pharmacology Team Leader	Suresh Doddapaneni, Ph.D.
Pharmacometrics Reviewers:	Christoffer W. Tornoe, Ph.D.
Pharmacometrics Team Leader:	Joga Gobburu, Ph.D.
Type of Submission:	Standard
Submission Date:	December 6, 2007
PDUFA Date:	October 5, 2008

Table of Contents

1 Execute Summary

The key pharmacometric findings from Cimzia BLA 125271 submission for treatment of rheumatoid arthritis are:

- There is clear evidence of exposure-response relationship for effectiveness (ACR-20 at week 24) for CDP870 using steady-state CDP870 trough concentrations (C_{trough}) as the exposure variable.

- Body weight was found to be a significant covariate for CDP870 clearance. However, the proposed fixed dosing regimen, i.e. not body weight corrected, is appropriate since the probability of ACR-20 response was found to be around 70% across all body weight quartiles due to a shallow body weight – exposure relationship and high enough exposures at the proposed dosing regimen.

- The formation of antibodies is inversely proportional to the CDP870 dose and exposure resulting in a 3-fold increase in CDP870 clearance for antibody positive patients. The ACR-20 response rate is reduced to around 40% for antibody positive patients.

- The proposed loading dose of 400 mg q2w + MTX at weeks 0, 2, and 4 is justified based on the identified exposure-response relationship for ACR-20 at week 12, which makes it desirable to get the CDP870 concentration levels faster to steady-state levels by administering a loading dose thereby increasing the probability of an earlier onset of action. Furthermore, the probability of developing antibodies was found to decrease with increasing concentrations and was also found to be irreversible thus supporting loading the patients with higher doses to reduce the probability of developing antibodies.

- The maintenance dose of 200 mg q2w + MTX is appropriate and results in ACR-20 response rates around 70% which is similar to previously approved biologics.

- The alternative proposed maintenance dose regimen of 400 mg q4w without MTX is not appropriate because:
  - Shifting from 200 mg q2w to 400 mg q4w dosing (same monthly dose) will result in lower ACR-20 response rates due to lower C_{trough} (ACR-20 response rate of 70% for q2w dosing compared to 50% for q4w dosing).
  - Shifting from co-administration of MTX to monotherapy will increase the antibody formation from 6% to 20% resulting in lower probability of ACR-20 response due to lower C_{trough}.

- Patients with concomitant administration of analgesics were found to have lower ACR-20 response rates of 55% compared to 68% without analgesics. US patients had 10% lower ACR-20 response rates compared to non-US patients. These identified differences in response rates were not found to be due to differences in exposure.

- There is an increase in risk for infection & infestations in patients receiving CDP870, as compared with patients receiving placebo. There was no significant difference in the incidence of infections & infestations between the MTX and non-MTX population. Exposure-safety relationship for infections (upper and lower respiratory tract, urinary, and herpes viral infections) was identified with the maximal CDP870 concentration (C_{max}) as a measure of exposure. However, the most frequent infections were those most often seen in the general population and were easily resolved thus not requiring CDP870 dose adjustments.

2 Introduction

Cimzia (Certolizumab pegol) is an anti-Tumour Necrosis Factor (TNF), genetically engineered humanized antigen binding fragment (Fab'), derived originally from murine hybridoma, manufactured by a bacterial expression system using *E. Coli.*

The sponsor has submitted the BLA to seek the indication for treatment of adults with active rheumatoid arthritis (RA).

The BLA includes one dose-finding study (CDP870-04) and four pivotal phase III studies (CDP870-011, -014, -027, and -050) in patients with RA. Furthermore, a population pharmacokinetic (PK) study report (CDP870-068) and exposure-response modeling report (CDP870-079) were included to investigate the covariate effects on PK and ACR-20 response.

3 Reviewer's Comments on Sponsor's Analyses

Sponsor's population PK and exposure-response analyses are summarized in Appendix (see section 5.1 and 5.2).

3.1 Population PK Analysis

Sponsor evaluated the effect of age, gender, concomitant medications (treatment with methotrexate, DMARDS, corticosteroids, NSAIDs, analgesics), laboratory of assay, on the pharmacokinetics of certolizumab pegol in subjects with rheumatoid arthritis.

Only body weight and the presence of anti-antibodies significantly influenced the pharmacokinetics of certolizumab. Extreme body weights of 40 kg and 120 kg are predicted to have an effect of approximately ±30% on clearance relatively to a 70 kg reference body weight. Anti-certolizumab antibody formation was associated with a 2.91-fold increase in clearance resulting in a 60% decrease in AUC, a 46% decrease in C_{max} and a 82% decrease in C_{min}.

Certolizumab volume of distribution was affected by concomitantly administered methotrexate, DMARDs, analgesics. Population PK analysis, which took into account PK data from clinical efficacy studies #027 and #050, confirmed the absorption differences noted between the lyophilized formulation and the solution in BE study CDP870-038.

3.2 Exposure-Response Analysis

Overall, the sponsor did a very extensive and thorough job characterizing Cimzia's exposure response relationship for effectiveness.

The sponsor used the average plasma concentration predicted for the individual subject during the dose interval (C_{avg}) because it provided a better exposure-response model fit than the plasma concentrations at the time of observation, regardless of the dose interval (2 or 4 weeks).

Sponsor found that the C_{avg} during the dose interval was similar for both the 200 mg q2w and 400 mg q4w dose regimens. Sponsor's C_{avg}–ACR-20 model predicted similar response probabilities for q2w and q4w dosing schedules (response rate of 0.71 vs. 0.69, respectively).

These observations do not correspond well with the observed ACR-20 response rates of 50% and 70% when shifting from 400 mg q4w + MTX to 200 q2w +MTX. The exposure-response data are therefore reanalyzed using the C_{trough} as the response variable to better capture the change in response rates with different dosing frequencies.

4 Reviewer's Analysis

The identified deficiencies in sponsor's analyses are addressed in reviewer's analysis below.

4.1 Is there evidence of exposure-response for effectiveness?

A clear dose-response relationship at week 12 is seen in the dose-ranging study 004 with doses from 50 – 800 mg q4w without concomitant MTX (see Figure 1).

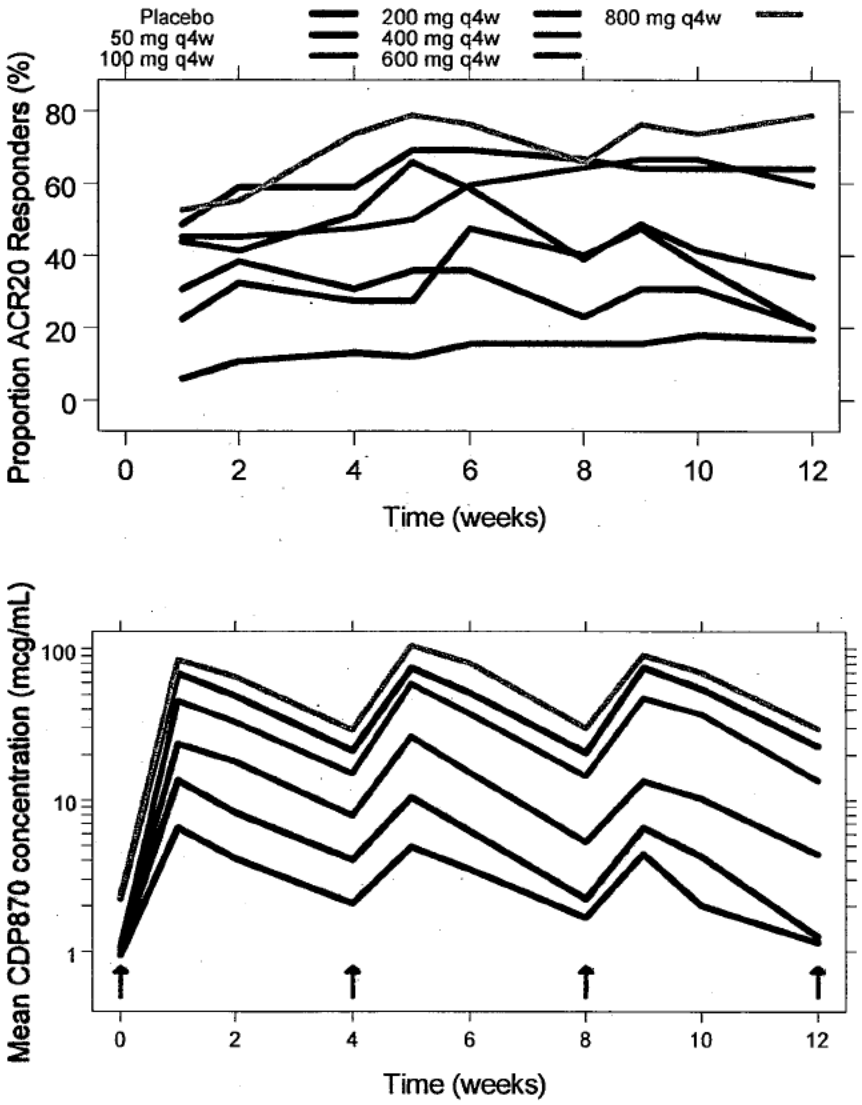

Figure 1. Proportion ACR-20 responders (top) and mean CDP870 concentration (bottom) time profiles for the dose-finding study 004 with doses ranging from 50-**800 mg** q4w without concomitant MTX. The black arrows illustrate time of dose administration.

The dose of 400 mg q4w was selected for the initial confirmatory studies 011 (without MTX) and 027 (with MTX) (see time course of ACR-20 response and PK in Figure 10). Both studies met their primary endpoint but the efficacy results were less than those seen with other studies of TNF blocking agents suggesting that the maximum effect may not have been reached.

Two additional confirmatory studies were conducted investigating the benefit of a 400 mg q2w loading dose on week 0, 2, and 4 followed by 200 mg q2w or 400 mg q2w with concomitant MTX (see time course of ACR-20 response and PK in Figure 8).

The ACR-20 response rates at week 24 from the four confirmatory trials are summarized in Table 1 across dose groups. The ACR-20 response rates increased from 50 to 70% when giving a loading dose and shifting from q4w to q2w dosing.

Table 1. ACR-20, ACR-50, and ACR-70 response rates for different dosing regimens tested in studies 011, 014, 027, and 050.

Week 24	Placebo	Placebo + MTX	400 mg q4w	400 mg q4w +MTX	200 mg q2w +MTX	400 mg q2w +MTX
ACR-20	15%	20%	50%	50%	68%	70%
ACR-50	5%	7%	23%	19%	38%	40%
ACR-70	0%	2%	5%	0%	21%	18%

There is clear evidence of exposure-response relationship for effectiveness (ACR-20 at week 24) for CDP870 using steady-state CDP870 trough concentrations (C_{trough}) on the log scale as the exposure variable (see Figure 2).

The overall ACR-20 response rate for placebo and CDP870 treated patients was 20% and 66%. Patients with C_{trough} > 10 mcg/mL had ACR-20 response rates above the overall response rate of 66%. The only dosing regimen that results in more than 90% of patients (antibody positive and negative) with C_{trough} > 10 mcg/mL is 400 mg q2w + MTX whereas 90% of patients receiving 400 mg q4w (- MTX) or 200 mg q2w + MTX had C_{trough} above 4 and 1 mcg/mL, respectively. For antibody negative patients only, the 10^{th} C_{trough} percentile for 400 mg q4w, 200 mg q2w +MTX, and 400 mg q2w + MTX is 3, 7, and 18 mcg/mL, respectively.

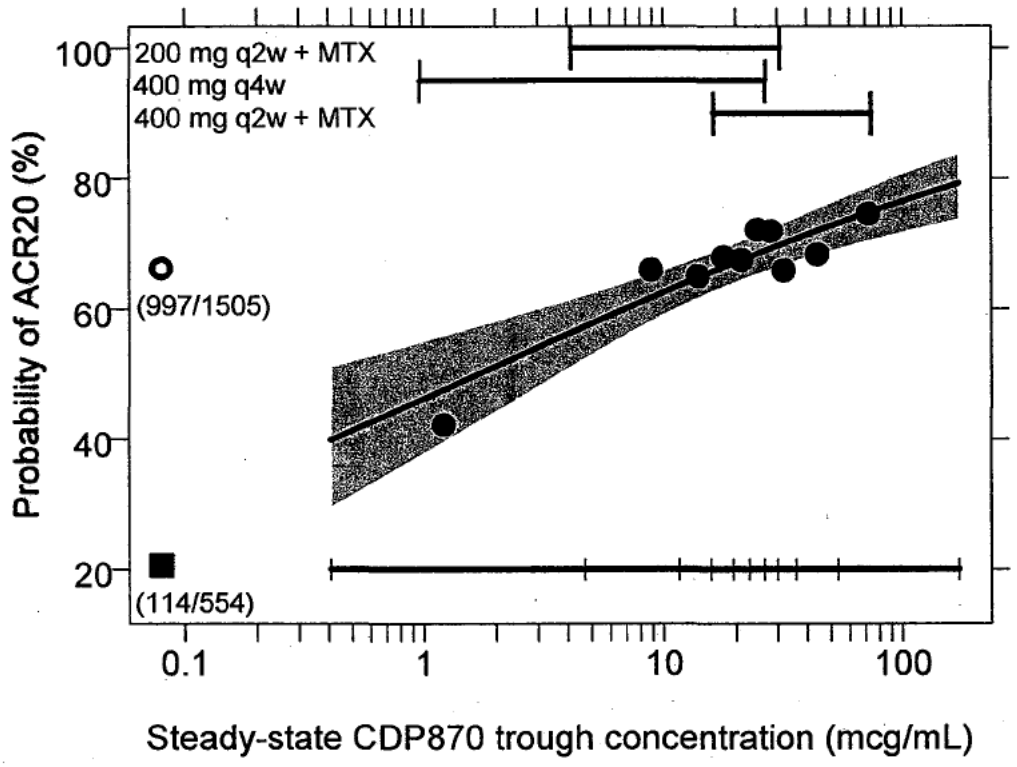

Figure 2. Exposure-response relationship for effectiveness at primary endpoint. Probability of ACR-20 response vs. steady-state CDP870 trough concentrations ($C_{ss,trough}$) at week 24 for studies 011, 014, 027, and 050. The overall CDP870 treated (open red circle) and placebo (solid black square) response rates are shown at the left hand side. The solid black line is the predicted ACR-20 response rate from the lowest to highest observed $C_{ss,trough}$ and the associated 95% CI (shaded area). The red dots represent the median $C_{ss,trough}$ in each decatile and the associated observed ACR-20 (LOCF) response rate. The colored horizontal bars represent the 10-90th CDP870 steady-state trough concentration percentiles for 200 mg q2w + MTX (orange), 400 mg q4w (blue), and 400 mg q2w + MTX (brown).

Patients with concomitant administration of analgesics were found to have lower ACR-20 response rates of 55% compared to 68% without analgesics. This identified difference in response rates was not found to be due to differences in exposure (see Figure 3 left).

US patients had 10% lower ACR-20 response rates compared to non-US patients (see Figure 3 right). A similar finding was observed in the Crohn's Disease studies.

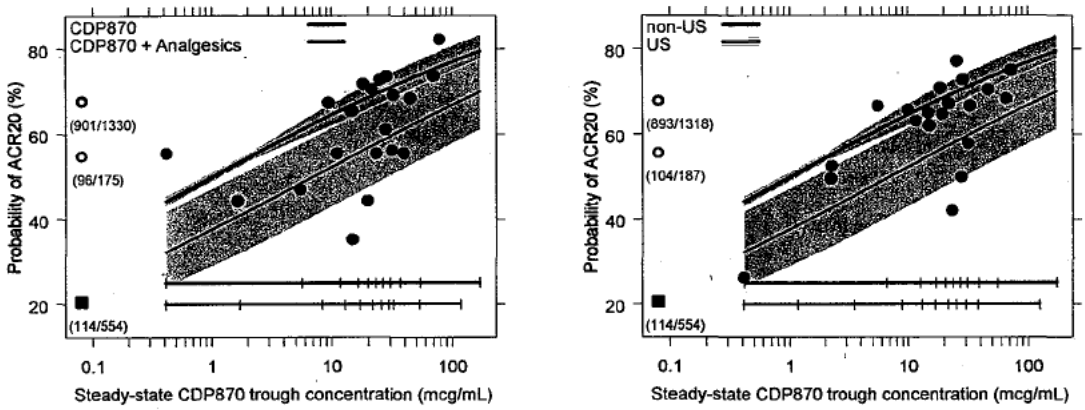

Figure 3. Exposure-response for **(left)** concomitant administration of analgesics and **(right)** geographical region (right). Probability of ACR-20 response vs. steady-state CDP870 trough concentrations ($C_{ss,trough}$) at week 24 for studies 011, 014, 027, and 050. The overall CDP870 treated without concomitant analgesics/non-US (open red circle) and with concomitant analgesics/US (open blue circle), and placebo (solid black square) response rates are shown at the left hand side of the figurs. The solid red and blue lines are the predicted ACR-20 response rate from the lowest to highest observed $C_{ss,trough}$ and the associated 95% CI (shaded area) for CDP870 treated with/without concomitant analgesics and US/non-US, respectively. The red and blue dots represent the median $C_{ss,trough}$ in each decatile and the associated observed ACR-20 (LOCF) response rate.

4.2 Is there evidence supporting one fixed dose for all patients?

Body weight and antibody status were identified as covariates for clearance in sponsor's population PK analysis with the latter being the major contributor to variability in clearance (see Figure 4).

Figure 4. (Left) Clearance vs. body weight for antibody negative (black circles) and positive (red crosses) patients with population predictions (red lines). **(Right) Box plot of** individual predicted clearances for antibody negative and positive patients together with population predictions (red lines).

The presence of antibodies (overall incidence of 12%) has a significant effect on the PK of CDP870. The population PK analysis showed that antibodies increased the clearance of CDP870 by 3-fold.

The increase in CDP870 clearance caused by antibodies results in a 46 % reduction in C_{max}, 82 % reduction in C_{trough}, and 60 % reduction in AUC for the dose interval. Body weight was found to have an effect of ±20% on C_{max}, ±50% on C_{trough}, and ±30% on AUC *(Source: Sponsor's report CDP870-068 page 62).*

Age, gender, concomitant treatment with methotrexate, DMARDS, corticosteroids, NSAIDS, analgesics, laboratory of assay did not significantly influence the PK of CDP870 in RA patients *(Source: Sponsor's report CDP870-068 page 62).*

Considerable variability in the exposure levels is observed following administration of a fixed dose of 200 mg q2w with observed CDP870 steady-state trough concentrations ranging between 0.5 and 115 mcg/mL (see Figure 5 (left)). Approximately 5% of the patients receiving 200 mg q2w in studies 027 and 050 had developed antibodies at week 24 resulting in lower steady-state CDP870 trough concentrations.

Fixed dosing, i.e. not body weight corrected dosing, is appropriate since the probability of ACR-20 response is 70% across all body weight quartiles for antibody negative patients as illustrated in Figure 5 (right) due to the shallow body weight – C_{trough} relationship and high enough exposures at the proposed dosing regimen.

In antibody positive patients, the ACR-20 response rate is reduced to around 40% (Figure 5, right). Due to the relative low incidence of antibodies, the overall effect of antibodies on efficacy is low. Since it is not feasible to measure patient's antibody status in a clinical setting, and the fact that antibody formation does not appear to be reversible with increased CDP870 dosing, a fixed dosing regimen (i.e. not body weight adjusted) is adequate.

In conclusion, the reviewer agrees with sponsor's proposal of a fixed, i.e. not body weight adjusted, dosing regimen of 200 mg q2w.

(b) (4)

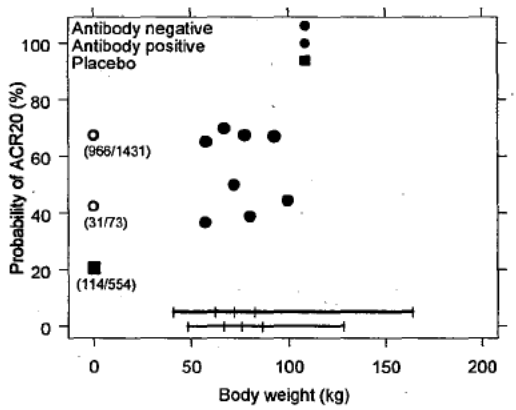

Figure 5. (Left) Steady-state CDP870 trough concentration vs. body weight for patients receiving 200 mg q2w in studies 027 and 050. The black dots and red crosses symbolize antibody negative and positive patients, respectively. **(Right)** Probability of ACR-20 response at week 24 for studies 027 and 050 vs. body weight. The red dots represent the median body weight in each quartile and the associated observed ACR-20 (LOCF) response rate.

4.3 What is the impact of antibody formation?

The formation of antibodies is inversely proportional to the CDP870 dose as illustrated in **Table 2** with 56% to 5% antibody positive patients receiving 50 to 800 mg q4w, respectively, in the dose-ranging study 004.

Table 2. Percentage antibody positive patients at week 12 across dose groups in dose-ranging study 004 administered q4w *(Source: Sponsor's immunogenicity report 400001600 p. 32).*

	50 mg - MTX (N=40)	100 mg - MTX (N=40)	200 mg - MTX (N=41)	400 mg - MTX (N=43)	600 mg - MTX (N=39)	800 mg - MTX (N=39)
% Antibody positive patients	**56**	**56**	**58**	**20**	**11**	**5**

The overall rate of antibody formation in the 4 Phase III studies at some point in the study was 7%. When co-administered with MTX, the incidence was 6% across all doses. When administered as monotherapy (400 mg q4w - MTX), the incidence of antibody formation was 20% (see Table 3).

Table 3. Overall antibody status at some point in the study across dose groups in phase III studies 011, 014, 027, and 050 *(Source: Sponsor's immunogenicity report 400001600 p. 32-36).*

	400 mg q4w - MTX (N=124)	400 mg q4w + MTX (N=124)	200 mg q2w + MTX (N=640)	400 mg q2w + MTX (N=633)
% Antibody positive patients	**20**	**5**	**10**	**2**

Antibodies start developing after 8 weeks of treatment and peaks after 12-16 weeks. A 3-fold increase in CDP870 clearance is seen for antibody positive patients reducing the CDP870 trough concentrations below 10 mcg/mL for the majority of antibody positive patients in studies 014, 027, and 050 utilizing background MTX.

The probability of developing antibodies is clearly increased in study 011 (without MTX) compared to study 014 (with MTX) where the only difference between the two studies is the concomitant administration of MTX in study 014 (see Figure 6). Unfortunately, PK samples were not collected past 24 weeks in study 011 to see the long term impact of antibodies on PK and ACR-20 response rates without concomitant MTX.

Figure 6. CDP870 concentration-time profiles in studies 011, 014, 027, and 050. The black dots and red crosses symbolize antibody negative and positive patients, respectively.

The probability of developing antibodies decreases with increasing CDP870 steady-state trough concentrations, i.e. the lower the CDP870 steady-state trough concentration, the higher the probability of having CDP870 antibodies (see Figure 7). Patients with CDP870 steady-state trough concentrations above 10 mcg/mL were found to have very little probability of developing antibody.

Only 400 mg q2w + MTX and 800 mg q4w dosing regimens result in 90% of patients having trough concentrations above 10 mcg/mL and thus very little antibody formation (see horizontal colored bars in Figure 7).

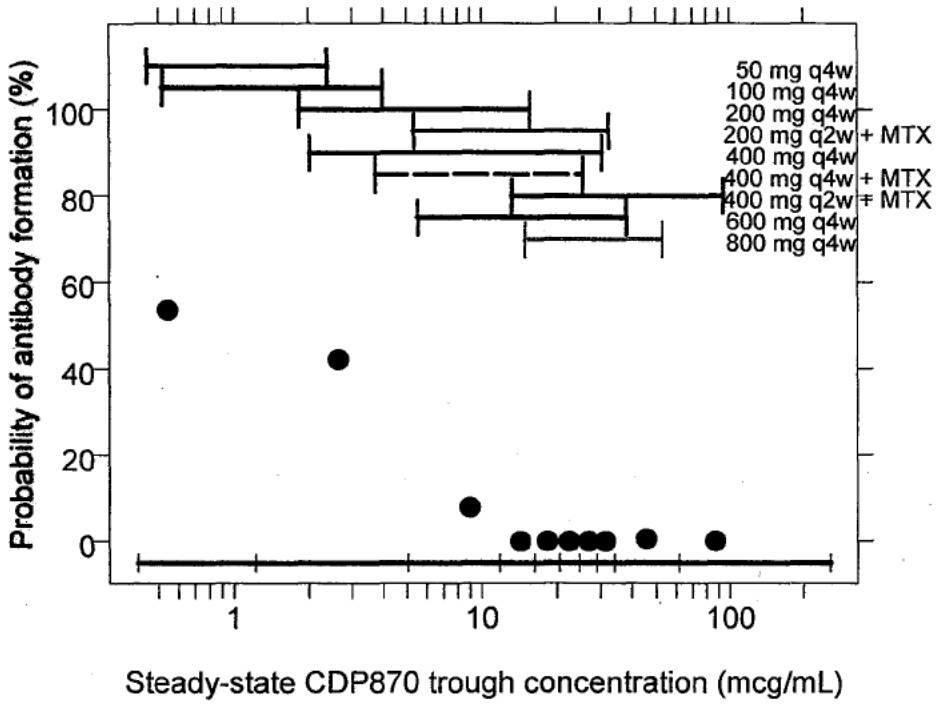

Figure 7. Probability of antibody formation vs. steady-state CDP870 trough concentration ($C_{ss,trough}$) from studies 004, 011, 014, 027, and 050. The horizontal colored bars represent the 10-90th $C_{ss,trough}$ percentiles for the different dosing regimens.

4.4 Is the appropriate loading dose identified?

The PK reaches steady-state levels around 4 weeks whereas the ACR-20 response is at steady-state around 12 weeks after initiation of CDP870 treatment (see Figure 8). It is thus difficult to separate out the effectiveness benefit of administering a loading dose of 400 mg q2w at weeks 0, 2, and 4 since the maintenance dose was also changed from 400 mg q4w in studies 011 and 014 to 200/400 mg q2w in studies 027 and 050.

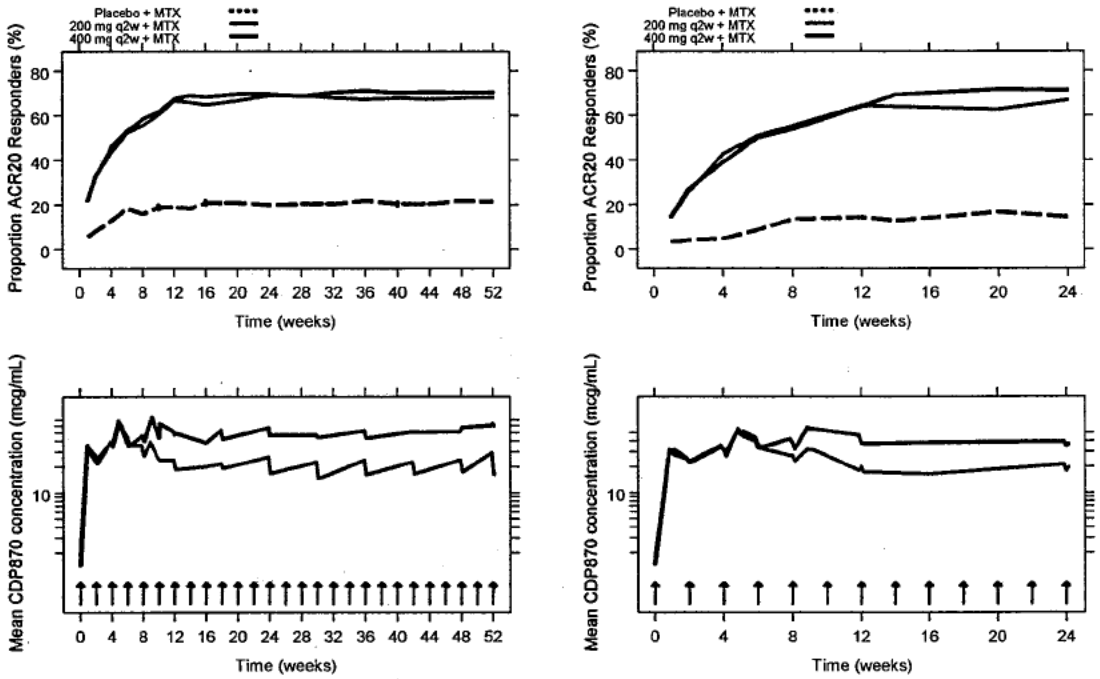

Figure 8. Proportion ACR-20 responders (top) and mean CDP870 concentration (bottom) time profiles for study 027 (left) and 050 (right). The ACR-20 response reaches steady-state around 12 weeks after initiation of treatment with the PK reaching levels above steady-state.

Predictions based on sponsor's PK/PD model showed that a loading dose would result in a typical 9% improvement in the probability of achieving an ACR 20 response rate at Week 12 following initiation of treatment compared with a non-loading dose regimen of 200 mg q2w. At Week 22, the predicted difference between the loading dose and the non-loading dose regimens was reduced to a 3% improvement in the probability of achieving an ACR 20 response. These predictions suggest that the main effectiveness benefit of the loading dose regimen is an improvement in speed of onset of ACR response predicted for the individual subject *(Source: Sponsor's report CDP870-079 page 95).*

An exposure-response relationship at week 12 was identified similar to the one at the primary endpoint (see Figure 9). The dosing regimen resulting in more than 90% of the patients attaining C_{trough} > 5 mcg/mL corresponding to the overall ACR-20 response rate of 60% at week 12 are 400 mg q2w + MTX at weeks 0, 2, and 4 followed by 200 mg q2w + MTX (orange line), 400 mg q2w + MTX (brown line) and 800 mg q4w (pink line).

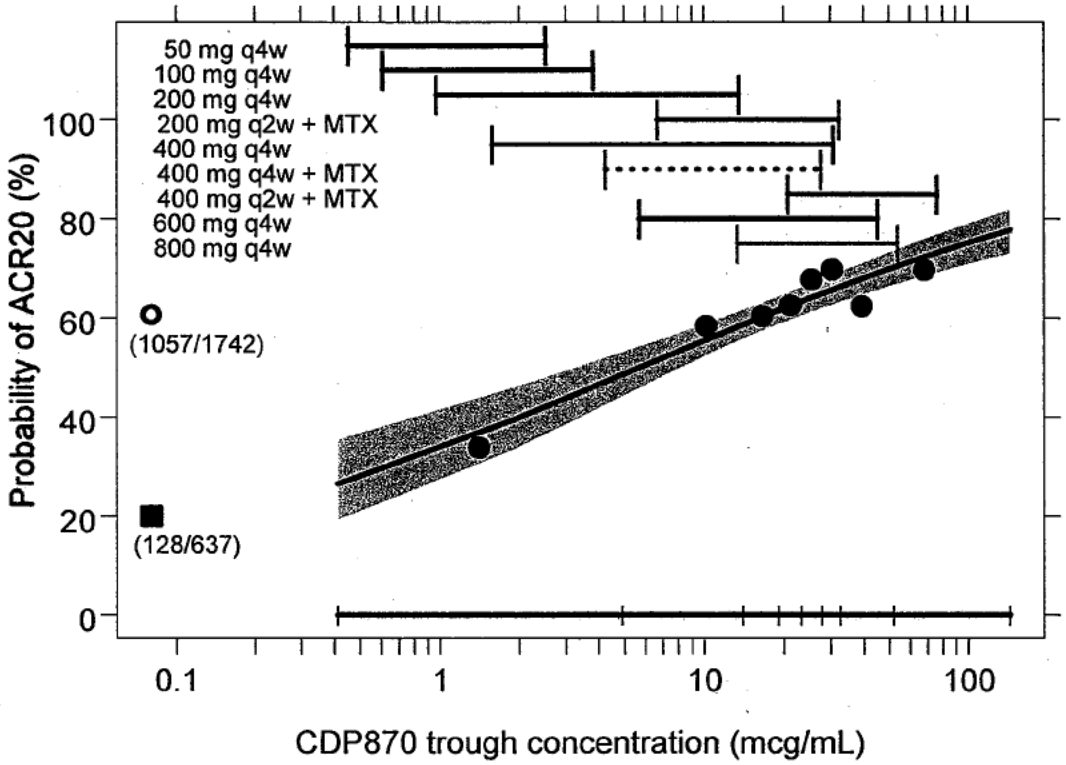

Figure 9. Exposure-response relationship for effectiveness at week 12. Probability of ACR-20 response (LOCF) vs. CDP870 trough concentrations for studies 004, 011, 014, 027, 050 at week 12. The horizontal colored bars represent the 10-90th C_{trough} percentiles for the different dosing regimens.

Since a clear exposure-response relationship was identified for ACR-20 at week 12, it is desirable to get the CDP870 concentration levels faster to steady-state levels by administering a loading dose thereby increasing the probability of an earlier onset of action. Furthermore, the probability of developing antibodies was found to decrease with increasing concentrations (see Figure 7) and was also found to be irreversible thus supporting loading the subjects with higher doses to reduce the probability of developing antibodies.

In conclusion, an initial 400 mg loading dose at weeks 0, 2, and 4 is appropriate.

4.5 Is the appropriate maintenance dose range identified?

The sponsor is asking for approval of 200 mg q2w as well as 400 mg q4w. Based on the identified exposure-response relationship, splitting the 400 mg q4w dose to 200 mg q2w increases the 10^{th} lowest C_{trough} percentile from 1 to 4 mcg/mL resulting in an increase from 50% to 70% in ACR-20 response (see Figure 2 and Table 1). The proposed alternative maintenance dose of 400 mg q4w should therefore not be approved.

There does not seem to be a benefit in ACR-20 response on a population level by increasing the maintenance dose from 200 mg q2w to 400 mg q2w. However, on an individual level, patients with higher CDP870 clearance might benefit from the higher 400 mg q2w dose which increases the lowest 10^{th} C_{trough} percentile from 4 to 10 mcg/mL.

A maintenance dose of 400 mg q2w also appears to be a valid option for patients not achieving ACR-20 response at e.g. week 12.

4.6 What are the benefits of co-administering Cimzia with methotrexate?

When looking at the primary endpoint (ACR-20 response at week 24) and the mean CDP870 concentration-time profile, MTX does not appear to have any major impact for CDP870 treated patients whereas there is a 5% increase in response rate for patients treated with placebo + MTX compared to placebo alone (see Figure 10 and Table 1).

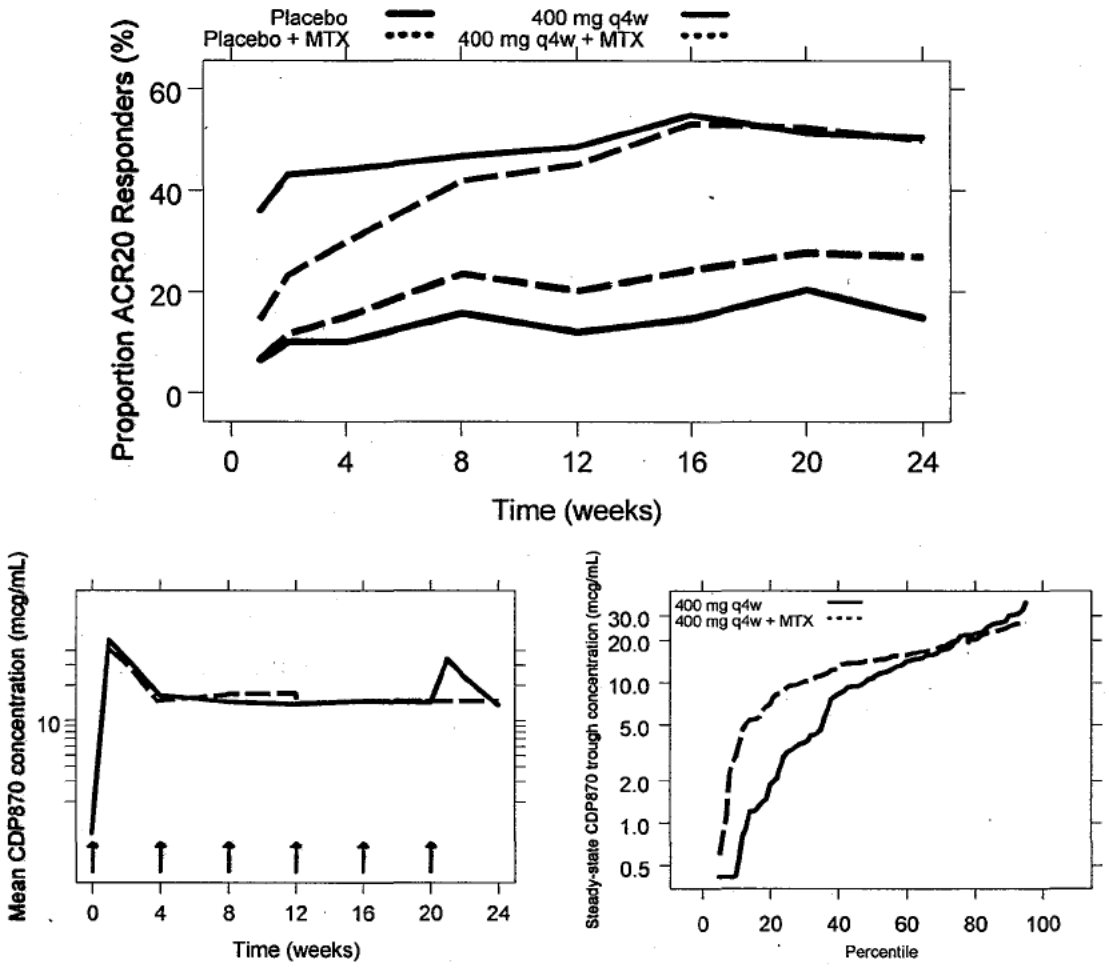

Figure 10. Proportion ACR-20 responders over time (top), mean CDP870 concentration-time profile (bottom left), and distribution of C_{trough} for studies 011 and 014 utilizing 400 mg q4w with (dashed lines) and without concomitant (solid lines) methotrexate (MTX), respectively.

However, there is an indirect benefit of concomitant MTX on the ACR-20 response rate by reducing the probability of antibody formation (see Table 3) which results in higher steady-state CDP870 trough concentrations (see Figure 7 and Figure 10 bottom right) and thereby higher probability of ACR-20 response (see Figure 2). Due to the relative low incidence of antibodies at 400 mg q4w, the indirect effect of concomitant MTX on ACR-20 is low (see Table 1).

4.7 Does the risk of infections increase with higher Cimzia exposure?

There is an increase in risk for infection & infestations in patients receiving Cimzia, as compared with patients receiving placebo (see Table 4). There was no significant difference in the incidence of infections & infestations between the MTX and non-MTX population.

Table 4. Percentage (number) of patients experiencing one or more infections and infestations and 4 high level terms.

	Placebo (N=647)	200 mg q2w + MTX (N=640)	400 mg q2w + MTX (N=635)	400 mg q4w (N=278)	All doses (N=1774)
Infections & Infestations	22.9% (148)	37.3% (239)	37.6% (239)	37.1% (103)	37.6% (667)
Upper respiratory tract infections	9.4% (74)	16.7% (107)	15.9% (101)	19.8% (55)	17.6% (313)
Urinary tract infections	4.5% (29)	6.3% (40)	7.2% (46)	2.2% (6)	5.8% (103)
Lower respiratory tract and lung infections	3.4% (22)	5.8% (37)	5.8% (37)	5.0% (14)	5.6% (100)
Herpes viral infections	1.2% (8)	3.1% (20)	4.1% (26)	3.6% (10)	3.6% (63)

Source : Table 8.1:10 in adverseevent.pdf on page 145-170

The most frequent infections were those typically seen in the general population, including upper respiratory tract infections, urinary tract infections, lower respiratory tract and lung infections, and herpes viral infections. In general, higher dose or dose frequency of Cimzia was not associated with an increased frequency of infections. No significant differences were observed between the 200 mg q2w and 400 mg q2w groups and the probability of infections.

Exposure-safety relationships were identified for infections & infestations (see **Figure 12**) as well as high level terms: Upper and lower respiratory tract, urinary, and herpes viral infections in studies 004, 011, 014, 027, 050 using C_{max} concentrations as a measure of exposure (see Figure 12). No dose adjustments are warranted since most infections were non-serious and easily resolved when treated.

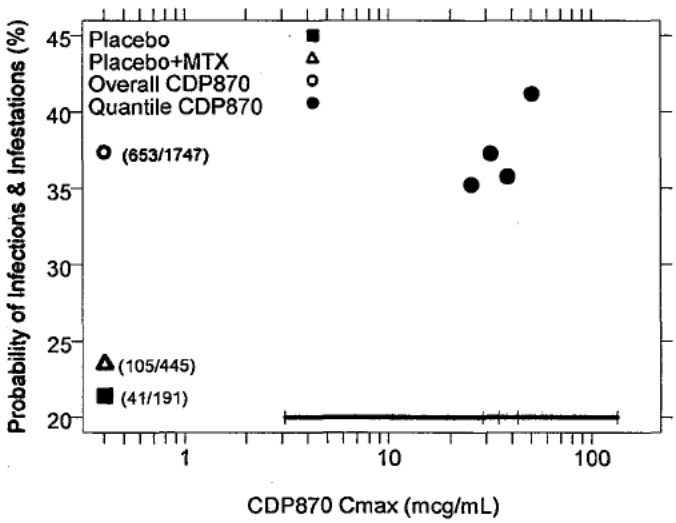

Figure 11. Exposure-response relationship for infections & infestations vs. CDP870 C_{max} concentrations.
Source: System organ class (mdsocnm) in ISS/AESAES.xpt.

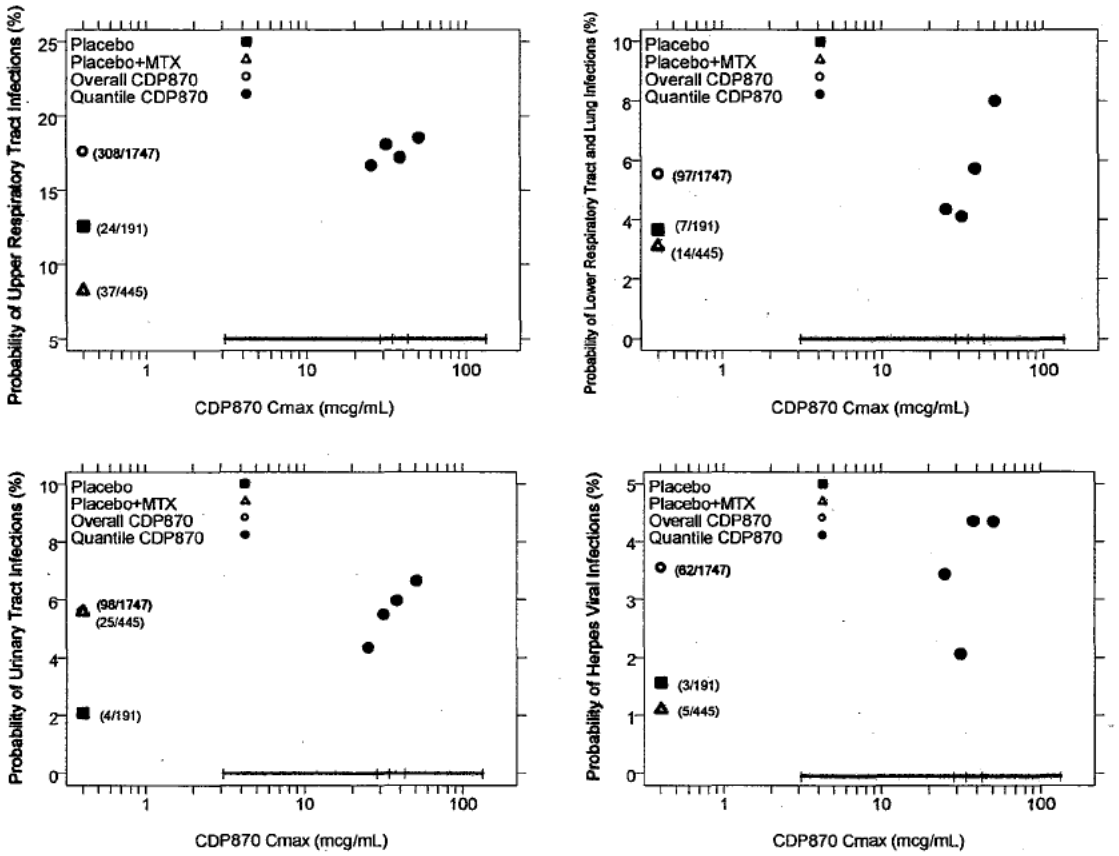

Figure 12. Exposure-safety relationship for upper respiratory tract and lung (top left), lower respiratory tract (top right), urinary tract (lower left), and herpes viral (lower right) infections (non-serious and serious) vs. CDP870 C_{max} concentrations.
Source: High level term (mdhltnm) in ISS/AESAES.xpt.

5 Appendix

5.1 Sponsor's Population Pharmacokinetic Analysis (CDP870-068)

Objectives

The primary objectives of the analysis were:

- To characterize the pharmacokinetics of certolizumab pegol in the RA population, including estimation of the inter-subject variability in the main pharmacokinetic parameters, using data pooled from 6 clinical trials.
- To identify important demographic and/or physiologic determinants of certolizumab pegol disposition in the RA population.

Study Design

Study PHA-001: open-label, non-randomized, single-dose, multi-center, pharmacokinetic study in patients with RA and under chronic treatment with methotrexate; dose 400 mg sc. A total of 22 post-dose samples per subject were collected.

Study CDP870-004: multi-center, double-blind, multiple dose, Phase II dose-ranging study in patients with RA; certolizumab pegol doses of 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, and 800 mg sc every 4 weeks from W0 to W8. A total of 9 post-dose samples per subject were collected.

Study CDP870-011: multi-center, double-blind, multiple dose, Phase III efficacy study in patients with RA; certolizumab pegol doses of 400 mg sc every 4 weeks from W0 to W20. A total of 12 post-dose samples per subject were collected.

Study CDP870-014: multi-center, double-blind, multiple dose, Phase III efficacy study in combination with methotrexate versus methotrexate alone in patients with RA; certolizumab pegol doses of 400 mg sc every 4 weeks from W0 to W20. A total of 11 post-dose samples per subject were collected.

Study CDP870-027: multicentre, double blind, multiple dose, 52-week Phase III efficacy study in combination with methotrexate versus methotrexate alone in patients with RA; certolizumab pegol doses of 200 mg (after an induction at 400 mg at week 0, 2 and 4) and 400 mg sc every other week. A total of 17 postdose samples per subject were collected.

Study CDP870-050: multi–center, double–blind, multiple dose, 24-week Phase III efficacy study in combination with methotrexate in RA patients; certolizumab pegol doses of 200 mg (after an induction at 400 mg at week 0, 2 and 4) and 400 mg sc every other week. A total of 10 post-dose samples per subject were collected.

Methods

Certolizumab pegol plasma concentration-time data were modeled by non linear mixed effects modeling using NONMEM. A one-compartment model with infusion time in the depot compartment, first order absorption and first order elimination was fitted to the

plasma concentration-time records. Inter-individual variability (IIV) was set on each structural parameter (absorption rate (ka), infusion time in the depot compartment (D1), apparent clearance (CL/F), apparent volume of distribution (V/F)) and was calculated as the square root of the variance for the respective parameter x100. Inter-occasion variability (IOV) was set on CL/F. A proportional error model for residual variability was assumed.

A baseline concentration term was included in the residual error model in order to account for potential bias in the immunoassay method. The effects of observed versus estimated baseline, of log-transformation of the data, and of FO versus FOCE-I estimation methods were evaluated during the development of the BASE pharmacokinetic model. The association between the following potential covariates and clearance and distribution volume was examined:

- CL/F: age, body weight, body surface area, body mass index, creatinine clearance, gender, ethnicity, antiantibody status, laboratory of assay, concomitant medications
- V/F: age, body weight, body surface area, body mass index, gender, antibody status, laboratory of assay, concomitant medications
- A formulation effect was also tested on F for the lyophilized formulation.

Number of subjects:
Data from 1768 RA patients were obtained and used for this population analysis, of whom 493 for the development dataset and 1275 for the validation dataset. There were 335 males and 1433 females with the following median (range) demographic covariates: age 53 (19-83) years, body weight 72 (41-164) kg, body mass index 26 (15-55) kg/m^2, body surface area 1.8 (1.3-2.7) m^2 , and creatinine clearance 98 (range: 30-218) mL/min.

Test Product, Dose and Mode of Administration:
Certolizumab pegol was administered subcutaneously using a (b) (4) 200 mg/mL solution (FORM=1, studies 001 and 004), a 10 mM pH 4.7 acetate buffered 200 mg/mL solution (FORM=4, study 050) or a 10 mM pH 5.2 lactate buffered 200 mg/mL lyophilized formulation (FORM=0, studies 011, 014 and 027).

Duration of Treatment:
The patients received a single dose of certolizumab pegol (study 001) or multiple dosing regimens for 8 weeks (monthly dosing, study 004), for 20 weeks (monthly dosing, studies 011 and 014), for 24 weeks (every 2 weeks dosing, study 050) and for 52 weeks (every 2 weeks dosing, study 027).

Main Measurements and variables:
Certolizumab pegol concentration-time data (plasma concentrations, actual sampling date and time). Covariate data: gender, weight, BSA, BMI, age, anti-certolizumab pegol antibody plasma concentrations, creatinine clearance, ethnicity, concomitant treatments (methotrexate, DMARDs, corticosteroids, NSAIDs, analgesics), laboratory of assay. Patients were flagged as antibody positive (Ab+) when the anti-certolizumab pegol concentration was greater than 2.4 U/mL.

Results

The model was developed using the 4 studies 001, 004, 011 and 014. Addition of a covariance term between clearance and volume substantially improved the goodness of fit. The formulation effect was removed during the covariate selection process. The covariate analysis evidenced statistically significant effects of antiantibodies and of bodyweight on CL/F, and of methotrexate on V/F. MonteCarlo simulations were performed to evaluate the clinical impact of these covariates: typical steady-state concentration-time profiles were simulated for a 200 mg dose every other week (eow) using extreme values of the dataset for bodyweight, and the main pharmacokinetic parameters (Cmax, AUCτ and Cmin) were calculated. They were compared to the reference population (RA patient of 70 kg, Ab- antibody status and not receiving methotrexate). These simulations showed that only the antibody status and bodyweight were clinically relevant, while methotrexate had a negligible effect and was subsequently removed from the model.

	AUC_τ (µg.day/mL)		C_{max} (µg/mL)		C_{min} (µg/mL)	
	Median	Ratio/ref	Median	Ratio/ref	Median	Ratio/ref
Reference subject: Ab-, 70 kg, MTX-	457	1	41	1	22	1
Ab+, 70 kg, MTX-	181	0.40	22	0.54	4	0.18
Ab-, 40 kg, MTX-	616	1.35	53	1.29	34	1.55
Ab-, 120 kg, MTX-	334	0.73	33	0.80	14	0.64
Ab-, 70 kg, MTX+	442	0.97	38	0.93	23	1.05

All the structural parameters of the final development model were estimated with good precision (17.3% or less). The IIV was moderate for V/F (30.6%) and for CL/F (30.9%; IOV: 23.8%). A larger inter-individual variability was found for ka (66.3%) and for D1 (61.7%).

During validation of the model using studies 027 and 050, it was found necessary to introduce a study specific factor on F for study 050 (FORM=4). The final pharmacokinetic model based on the overall dataset and including study specificity for study 050 was described by the following parameters:

$F_{FORM=4} = 0.811$
$k_a\ (day^{-1}) = 0.419$
D1 (day) = 0.507
V/F (L) = 8.01
$CL/F\ (L/day) = 0.505 \times (2.91)^{ABFL} \times (WT/71.5)^{0.6}$

In which ABFL=0 in Ab- (antibody negative) patients and =1 in Ab+ patients, and WT is body weight in kg. The presence of anti-antibodies (overall incidence = 12.0%) had the largest effect, increasing the clearance by 2.91-fold. Bodyweight affected clearance by approximately ±30% around the typical value, over the extreme weights of 40 and 120 kg.

Conclusions

The presence of anti-antibodies is associated with a 2.91-fold increase in clearance resulting in a 60% decrease in AUC, a 46% decrease in Cmax and a 82% decrease in Cmin. Extreme body weights of 40 kg and 120 kg are predicted to have an effect of approximately ±30% on clearance relatively to a 70 kg reference body weight.

Age, gender, concomitant treatment with methotrexate, DMARDs, corticosteroids, NSAIDs, analgesics, laboratory of assay, did not significantly influence the pharmacokinetics of certolizumab pegol in subjects with rheumatoid arthritis.

5.2 Sponsor's Exposure-Response Analysis (CDP870-079)

Objective

The objective of this population meta-analysis was to describe the exposure-response relationship of certolizumab pegol in patients with rheumatoid arthritis, using the changes in the ACR-20 clinical score as response variable.

Study Designs

Study CDP870-004: multi-center, double-blind, multiple dose, Phase II dose-ranging study in patients with RA; certolizumab pegol doses of 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, and 800 mg sc every 4 weeks for 8 weeks. A total of 9 post-dose samples per subject were collected. Clinical score recorded on Week (W) 1, 2, 4, 5, 6, 8, 9, 10 and 12.

Study CDP870-011: multi-center, double-blind, multiple dose, Phase III efficacy study in patients with RA; certolizumab pegol doses of 400 mg sc every 4 weeks for 20 weeks. A total of 12 post-dose samples per subject were collected. Clinical score recorded on W1, 2, 4, 8, 12, 16, 20 and 24.

Study CDP870-014: multi-center, double-blind, multiple dose, Phase III efficacy study in combination with methotrexate versus methotrexate alone in patients with RA; certolizumab pegol doses of 400 mg sc every 4 weeks for 20 weeks. A total of 11 post-dose samples per subject were collected. Clinical score recorded on W1, 2, 4, 8, 12, 16, 20 and 24.

Study CDP870-027: multi-center, double blind, multiple dose, 52-week Phase III efficacy study in combination with methotrexate versus methotrexate alone in patients with RA; certolizumab pegol doses of 200 mg (after an induction at 400 mg at week 0, 2 and 4) and 400 mg sc every other week. A total of 17 postdose samples per subject were collected. Clinical score recorded on W1, 2, 4, 6, 8, 9, 10, 12, 14, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52.

Study CDP870-050: multi-center, double-blind, multiple dose, 24-week Phase III efficacy study in combination with methotrexate in RA patients; certolizumab pegol doses of 200 mg (after an induction at 400 mg at week 0, 2 and 4) and 400 mg sc every other week. A total of 10 post-dose samples per subject were collected. Clinical score recorded on W1, 2, 4, 6, 8, 12, 14, 20 and 24.

Methods

Clinical scores (ACR-20) over time were modeled by non linear mixed effects modeling using NONMEM software. The ACR-20 scores and the dropout events where coded in 3 categories (0= ACR-20 not achieved, 1= ACR-20 achieved and 2=drop-out). The probability of the transitions between the 3 different stages was modeled using logit functions.

For a non-responder patient at a certain observation time, the 3 possible transitions to the next observation are "10" in case the patient becomes responder, "00" in case the patient

remains non-responder and "20" if the patient drops out of the study. Consequently the sum of the probabilities of these 3 transitions is equal to 1: Pr10+Pr00+Pr20=1. Similarly, for a responder patient at a certain observation time, the 3 possible transitions to the next observation are "01" in case the patient becomes non-responder, "11" in case the patient remains responder and "21" if the patient drops out of the study. As with the corresponding transition probabilities for nonresponders, the probabilities of these three transitions add to 1: Pr01+Pr11+Pr21=1.

The model was defined by structural parameters to estimate the probabilities Pr10, Pr01, Pr20 and Pr21. The probabilities Pr11 and Pr00 were deduced from the others. Inter-individual variability was included in the logit function for Pr10 and Pr01. Individual exposures to certolizumab pegol were obtained as post hoc estimates from a population pharmacokinetic model in the same patients (study CDP870-068). Two potential exposure measures were evaluated as potential explanatory variables for the exposure-response relationship for ACR-20, the concentration at the time of clinical observation (CONC) and the average concentration intervening between doses (Cavg). The variable that provided the best fit to the observed data was then selected as the exposure measure to be used in all subsequent model building.

The model was built in 3 steps: 1° Characterization of response time course for placebo subjects including covariate effects on all transitions; 2° Incorporation of drug data and modeling of exposure-response relationship; 3° Second round of covariate testing using the full dataset and the final model from step 2. The effect of the following potential covariates on each of the 4 transitions was examined:

- Demography: age, weight, gender, geographical region
- Concomitant medications: dose of methotrexate (MTX), use (Y/N) of corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics.
- Previous medications: number of previous disease-modifying anti-rheumatic drugs (DMARDs)
- Disease: disease duration, baseline ACR subscores (tender joint count (TJC), swollen joint count (SJC), physician and patient global assessments of disease activity, patient assessment of arthritis pain, patient assessment of physical function (HAQ-DI), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), average of previous ACR-20 scores and antepenultimate score.

Number of subjects

Data from 2380 RA patients (1747 on drug and 633 on placebo treatment) were obtained and used for this population analysis.

Demographics

There were 1925 females and 455 males with the following median (range) demographic covariates: age 53 (18-83) years, body weight 74 (41-164) kg. There were 2216 Caucasians, 78 Hispanics, 31 Afro-Caribbeans, 15 Far-east Orientals, 2 Asiatic Indians, 19 from other groups and 19 unknown. 363 patients were from North America, 463 from Western Europe, 740 from Eastern Europe, 153 from Central and South America, 591 from Northern Europe and Baltic States, and 70 from Asia/Oceania.

Test Product, Dose and Mode of Administration
Certolizumab pegol was administered subcutaneously using a [redacted] (b) (4) 200 mg/mL liquid (FORM=1, study 004), a 10 mM pH 5.2 lactate buffered 200mg/mL lyophilized formulation (FORM=0, studies 011, 014 and 027) or a 10 mM pH 4.7 acetate buffered 200 mg/mL liquid (FORM=4, study 050).

Duration of Treatment
The patients received multiple dosing regimens for 8 weeks (every 4 weeks, study 004), 20 weeks (every 4 weeks, studies 011 and 014), 24 weeks (every other week, study 050) and 52 weeks (every other week, study 027).

Main Measurements and variables
Efficacy measurement: ACR-20 responder status (ACR-20 scores, actual observation dates and times) Exposure (from the pop PK model CDP870-068): CONC (individual concentration estimated at the time of clinical observation) and Cavg for the interval between two consecutive doses (area under the individually predicted concentration-time curve divided by the duration of the dosing interval).

Covariate data: race, age, weight, gender, geographical region, concomitant use of steroids, NSAIDs and analgesics, dose of MTX at inclusion, number of previous DMARDs used, disease duration at inclusion, baseline ACR sub-scores (tender joint count, swollen joint count, physician and patient global assessment of disease activity, patient assessment of arthritis pain, patient assessment of physical function (HAQ-DI), CRP and ESR).

Results
The model was developed using the 5 studies 004, 011, 014, 027 and 050. The decrease of Pr01 over time was described by an Emax function on the logit scale and increase of Pr10 over time by a linear function on the logit scale. The exposure metric Cavg was chosen because it yielded a better fit than the CONC.

The decrease of Pr01 and increase of Pr10 as a function of Cavg were described by Emax functions on the logit scale, whereas the decreases of the dropout probabilities Pr20 and Pr21 with Cavg were described by linear functions (with the same slope) on the logit scale.

The Cavg corresponding to half the maximum Pr10 and half the minimum Pr01 transition probabilities (C50) was estimated at 16.8 µg/mL (95%CI [10.2-23.4]).

The covariate analysis indicated that the following covariates statistically significantly (p=0.01)

- increased Pr01: geographical region (North America [NA]), age
- decreased Pr01: average of previous ACR-20 scores (AVSC), baseline patient's assessment of arthritis pain (BPAP)
- increased Pr10: AVSC, antepenultimate score (SND), baseline CRP (BCRP)
- decreased Pr10: baseline tender joint count
- increased Pr20: geographical region (NA), AVSC, disease duration
- decreased Pr20: gender
- increased Pr21: geographical region (NA)
- decreased Pr21: AVSC

The clinical relevance of each covariate effect was determined by evaluating the magnitude of its influence on transition probability. For each included covariate, all covariate effects except the tested one were omitted in the model and the resulting transition probabilities over a range (0.1 to 0.9) for the baseline transition probability were computed. For categorical covariates, the difference between these probabilities and the baseline probabilities was then computed, whereas for continuous covariates, the difference in the transition probability using the extreme values of the covariate in the dataset was computed. Covariates which produced a maximum absolute difference in probability of less than 10% (i.e. use of NSAIDs and geographical region on P10, dose of MTX on P20) were removed from the model.

Transition	Covariate	Max difference in the probability	Associated baseline probability
01	AVSC	-0.50	07-0.8
	Age	0.15	0.4
	BPAP	-0.13	0.5-0.6
	Region (NA)	0.10	0.4-0.5
10	AVSC	0.25	0.3-0.4
	BCRP	0.22	0.3-0.4
	SND	0.15	0.4-0.5
	BTJC	-0.10	0.5-0.6
20	AVSC	0.50	0.2-0.3
	Disease duration	0.26	0.3-0.4
	Region (NA)	0.26	0.4
	Gender (males)	-0.11	0.5-0.6
21	AVSC	-0.50	0.7-0.8
	Region (NA)	0.27	0.4

Covariates that increase Pr10 enhance the probability of a non-responder becoming a responder and consequently covariates that decrease Pr10 enhance the probability of a non-responder remaining a nonresponders. Similarly, an increase in Pr01 makes it more likely for a responder to switch back to being a nonresponder while a decrease in Pr01 enhances the probability of remaining responder.

All parameters from the final model were estimated with good precision :

- 5.1% to 36.2% for structural parameters
- 13.2 and 14.9% for inter-individual variability
- 8.28% to 39% for covariate effects.

The model was validated using the predictive check method, which confirmed its capability to simulate results ACR-20 response rates similar to the observations for the following dosing regimens: 200 or 400 mg every other week (Q2wk) lyophilized or liquid (b) (4), 200 or 400 mg Q2wk liquid (pH=4.7) formulation, 200 or 400 mg Q2wk lyophilized formulation, placebo Q2wk or every 4 weeks (Q4wk).

The model was then used to predict the performance of various treatment regimens in a variety of hypothetical patient populations. The impact of body weight and antibody status was evaluated, as both had been identified as significant covariates in the population pharmacokinetic model.

The median response rates (from 1000 simulations) by treatment for the combination of most extreme body weight populations (BW > 95%), antibody-negative (Neg) and -positive (Pos) populations as well as the corresponding reference population are reported in the following table:

Week	Treatment	Predicted ACR-20 Response Rate		
		BW<95%; Neg	BW>95%; Neg	BW>95%; Pos
12	Placebo	0.31	0.29	0.28
	200 mg lig. Q2wk	0.55	0.50	0.38
	200 mg lyoph. Q2wk	0.60	0.56	0.41
	400 mg liq. Q4wk	0.57	0.51	0.39
	400/200 mg liq. Q2wk	0.64	0.60	0.42
	400 mg liq. Q2wk	0.71	0.64	0.47
24	Placebo	0.37	0.35	0.35
	200 mg lig. Q2wk	0.68	0.61	0.47
	200 mg lyoph. Q2wk	0.71	0.67	0.49
	400 mg liq. Q4wk	0.69	0.64	0.48
	400/200 mg liq. Q2wk	0.71	0.67	0.49
	400 mg liq. Q2wk	0.78	0.73	0.58

Conclusions

In conclusion, a significant exposure-response relationship was demonstrated for certolizumab pegol in rheumatoid arthritis. The best model combined Emax functions depending on Cavg in the logit functions related to the probabilities to become responder (Pr10) and to become non-responder (Pr01), and a linear dependence on Cavg in the logit functions related to the dropout probabilities Pr20 and Pr21. This model adequately described the observed data. From the C50 model estimates for the transition probabilities Pr01 and Pr10, typical Cavg producing half the maximum increase (decrease) to become a responder (non-responder) on the logit scale was estimated to 17 µg/mL (95%CI [10-23]).

Non-responder patients with a high average of previous ACR-20 scores, a high baseline CRP or who were responders at the antepenultimate visit were more likely to become responder at the next visit. Responder patients with high average of previous ACR-20 scores or a high baseline self-assessment of arthritis pain were more likely to remain responder.

Non-responder patients with a high baseline tender joint count were more likely to remain non-responder. Older responder patients and responder North Americans were less likely to remain responder . Concerning the drop-out rates, North-Americans, patients with longer disease duration and patients with high average of previous ACR-20 scores were more likely to drop-out from non-responder status. Males were less likely to dropout from non-responder status. North Americans are more likely to dropout from responder status as well and a high average of previous ACR-20 scores decreased the probability to drop-out from responder status.

4.2 Proposed labeling

See attached

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Study Synopsis CDP870-003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: **December 24, 2008**

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

Donna Griebel, MD , Director
Division of Gastrointestional Products (DGP)

Through: Claudia Karwoski, PharmD, Director (Acting) for C. Karwoski 12/24/08
Division of Risk Management (DRISK)

From: **OSE Cimzia REMS Review Team**
Scientific Lead: Doug B. Pham, PharmD, JD, Drug Risk Management Analyst, (DRISK) 12/24/08
Team Members:
Marcia Britt, PhD., Health Education Reviewer (DRISK)
Peter Diak, Pharm.D., MPH, Safety Evaluator, Division of Pharmacovigilance (DPV) II
Jodi Duckhorn, MA, Patient Labeling and Education Team Leader (DRISK)
Kate Heinrich, MA, Health Education Reviewer (DRISK)
Brian Gordon, MA, Social Science Reviewer (DRISK)
Mary Willy, Ph.D, Team Leader (Acting), Senior Drug Risk Management Analyst, (DRISK)
Kathleen Klemm, Regulatory Review Officer, Professional Review Group III, Division of Drug Marketing, Advertising and Communications (DDMAC)
Shefali Doshi, Consumer Safety Officer, Direct-to-Consumer Review Group I, (DDMAC)

Subject: Review of Risk Evaluation and Mitigation Strategy (REMS)

Drug Names: Cimzia® (certolizumab pegol)

Application Type/Number: BLA 125271 and BLA 125160

Applicant/sponsor: UCB, Inc.

OSE RCM #: 2008-1632

1 INTRODUCTION

This review follows a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Risk Evaluation and Mitigation Strategy (REMS) for Cimzia (certolizumab pegol).

The proposed REMS will modify the currently approved Cimzia REMS for BLA 125160 and will be a component of the pending review for BLA 125271 by DAARP.

2 BACKGROUND

Cimzia (certolizumab pegol, BLA 125160), a Tumor Necrosis Factor (TNF) blocking agent, was originally approved on April 22, 2008 by the Division of Gastroenterology Products (DGP) for reducing the signs and symptoms of Crohn's Disease (CD) and maintaining clinical response in adult patients with moderately to severely active disease who have an inadequate response to conventional therapy. A REMS was required as part of the approval and included only a Medication Guide and a timetable for assessment of the REMS.

Prior to the approval of BLA 125160, the Sponsor (UCB, Inc.) submitted an application for Cimzia (certolizumab pegol, BLA 125271) seeking a new indication for rheumatoid arthritis (RA). The review of BLA 125171 was delayed due to new safety information concerning serious fungal infections that required modifications to the current REMS for BLA 125160.

On September 4, 2008, DGP notified the Sponsor that the current labeling and Medication Guide only REMS did not adequately warn healthcare providers and patients about the increased risk of invasive fungal infections, specifically histoplasmosis, with concomitant TNF blocker use. The Sponsor was advised of required safety labeling changes including a boxed warning describing the increased risk for serious infections, particularly fungal infections. In addition, the Sponsor was informed that an updated REMS was required, which included a Medication Guide, a communication plan, and a timetable for assessment of the REMS.

On September 24, 2008, DAARP notified the Sponsor that the review of BLA 125271 was being delayed as a result of the recent safety information described previously. DAARP recommended a proposed REMS for both BLAs 125160 and 125271 and noted that if such submission was received prior to October 3, 2008 (PDUFA date for BLA 125271), DAARP would consider such submission as a major amendment in extending the review clock.

The Sponsor submitted a proposed REMS for Cimzia (BLA 125160 and 125271) on September 30, 2008 and FDA issued comments on December 16, 2008. The Sponsor submitted a revised REMS proposal on December 18, 2008.

3 MATERIAL REVIEWED

- Approved REMS for Cimzia (BLA 125160) dated April 22, 2008.
- Proposed REMS for Cimzia (BLA 125271 and 125160) dated September 30, 2008.
- Mills S. Review of Patient Labeling (Medication Guide), BLA 125271 and 125160, dated October 21, 2008.
- Modified Proposed REMS for Cimzia (BLA 125271 and 125160) dated December 18, 2008.

4 PROPOSED REMS

4.1 Goals

The FDA and Sponsor's agreed upon REMS goal is:

To communicate and mitigate the risks associated with CIMZIA therapy by:

- Alerting and warning healthcare providers of the recent cases for unrecognized histoplasmosis and other invasive fungal infections associated with concomitant Tumor Necrosis Factor (TNF) blocker use.
- Educating patients about the risks associated with CIMZIA therapy for serious infections including tuberculosis (TB) and infections caused by viruses, fungi, and bacteria spreading throughout the body.

4.2 REMS Elements

The REMS includes a Medication Guide, communication plan, and a timetable for assessment with the information needed for assessment. Each element is described below and the final formatted REMS is presented in Appendix A.

4.2.1 Medication Guide

A review of the proposed Medication Guide (MG)[1] was conducted and comments were provided to the Sponsor on December 5, 2008. The Sponsor has accepted all comments and has submitted a revised MG with the modified REMS proposal (dated December 18, 2008).

The updated MG will be used for the next production run of finished products (Cimzia Kits). Based on current inventory, the Sponsor estimates Cimzia Kits containing the updated MG will be available mid-February 2009.

A MG will be dispensed with each CIMZIA kit in accordance with 21 CFR 208.24. Each Cimzia kit contains the product's approved package insert (labeling) and MG.

[1] Mills S. Review of Patient Labeling (Medication Guide), BLA 125271 and 125160, dated October 21, 2008.

If a Cimzia kit is dispensed (lyophilized powder for reconstitution) and the drug is administered by a healthcare professional, the MG will be provided by the healthcare professional. Further copies of the MG may be provided by Medical Science Liaisons (MSLs) and sales representatives to healthcare professionals if necessary.

4.2.2 Communication Plan

The Sponsor will implement a communication plan to healthcare professionals (HCPs), especially gastroenterologists, rheumatologists, and other specialists (e.g. internal medicine and family medicine) who may potentially prescribe TNF blockers, by conveying the following information:

- The risk of developing invasive fungal infections, including histoplasmosis, coccidioidomycosis, blastomycosis, and other opportunistic fungal infections while treating with TNF blockers
- Provide descriptive information on the signs and symptoms of fungal infections, including histoplasmosis.
- Provide references and background information regarding the treatment of these infections.

This element of the REMS is not intended to continue over the lifetime of the product; it will function only to disseminate the new safety information about histoplasmosis and other invasive fungal infections associated with TNF blocker use.

The communication plan includes a Dear Healthcare Provider Letter, web-based materials to inform healthcare providers and patients, and a Medical Scientific Liaison slide deck.

4.2.2.1 *Dear Healthcare Provider Letter*

The sponsor will disseminate a Dear Healthcare Provider Letter within 60 days of the REMS approval. The purpose of this letter is to inform healthcare providers of the risk for developing invasive fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, and other opportunistic fungal infections while treating with TNF blockers, the signs and symptoms of possible systemic fungal infections, the need to suspect fungal infection in symptomatic patients who live or travel to endemic regions, and the need to reevaluate the benefit/risk prior to restarting TNF blocker therapy after recovery of an antifungal infection.

The letter references FDA links to provide more information and lists contact information for reporting cases of serious fungal infections or serious adverse events associated with the use of Cimzia.

UCB will disseminate the Dear Healthcare Provider Letters through First Class US mail and target U.S. healthcare providers in the following specialties: gastroenterology, internal medicine, family medicine, emergency medicine, and infectious disease

specialists in the endemic areas of the Ohio and Mississippi River valleys and San Joaquin valley.

4.2.2.2 *Web-based Materials to Inform Healthcare Providers and Patients*

The Sponsor will develop a stand-alone link on the existing www.CIMZIA.com website entitled, "Important Safety Information Regarding Fungal Infections," within 60 days of the REMS approval. This website will describe the REMS program and provide links or display the Dear Healthcare Provider Letter, approved MG, approved package insert, and approved Medical Science Liaison (MSL) slide deck. The website will also provide a brief summary describing the occurrence of histoplasmosis and other fungal infections.

The UCB www.CIMZIA.com website will be available to all healthcare providers as it is in the public domain and UCB sales representatives and MSLs will encourage healthcare providers to visit the information.

4.2.2.3 *Medical Scientific Liaison Slide Decks (Safety-related)*

The Sponsor will develop a specific dedicated slide-deck to inform healthcare providers about the occurrence of unrecognized histoplasmosis and other invasive fungal infections to be used by Medical Scientific Liaisons (MSLs). The slide-deck will be used to highlight key safety information and introduce the REMS to all Gastroenterology Key Opinion Leaders (approximately 500).

4.2.3 Elements to Assure Safe Use

The REMS does not include any Elements to Assure Safe Use.

4.2.4 Assessment of the REMS

The sponsor will submit a REMS Assessment to FDA at the following timetables:

1st FDAAA Assessment:	November 2009
2nd FDAAA Assessment:	May 2011
3rd FDAAA Assessment:	May 2015

The sponsor is required to submit assessments within 60 days of the noted time intervals.

Information needed for assessment is not a required element of the REMS Proposal. However, this information should be addressed in the REMS approval letter and discussed in the REMS supporting documents.

Information needed for assessment will include but is not be limited to:

A. Information specified in the initial REMS approval including:
    a. Survey of patients' understanding of the serious risks of CIMZIA ™

b. Report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

B. [redacted]

As described in the information needed for assessment, the Sponsor will conduct both a healthcare provider and patient survey. The Sponsor plans to conduct pre-testing of the survey questions, which may alter and change current survey questions. As such, we recommend the Sponsor submit and note any changes within survey protocols and sample questions to FDA 60 days prior to conducting the survey.

The target dates for the submitting survey reports are described in the above assessment timetables. Each survey type is discussed below.

A. Patient Survey:

The Sponsor will conduct an [redacted] patient survey [redacted] to assess patient understanding of the serious risks of using Cimzia. The study design, methodology, and sample survey questions have been reviewed and comments have been provided to the Sponsor. The Sponsor has accepted all recommendations and the current patient survey is acceptable.

B. Healthcare Provider Survey:

The sponsor will conduct a healthcare provider survey [redacted] to assess provider awareness of the risks (histoplasmosis and other invasive fungal infections) associated with the use of Cimzia. [redacted] The study design, methodology, and sample survey questions were submitted with the modified REMS proposal, and no comments have been provided to the Sponsor.

[redacted]

5 CONCLUSIONS AND RECOMMENDATIONS

The Division of Risk Management in the Office of Surveillance and Epidemiology find the proposed REMS for Cimzia (certolizumab pegol) acceptable in accordance to the statutory requirements of 21 CFR 208 and FDCA 505-1. We have the following recommendations and comments:

1. Please see attached REMS Template for additional track changes corresponding to comments in this review.
2. The MG content and distribution procedure is acceptable.
3. The proposed Communication Plan (Dear HCP Letter, website, and MSL slide-deck) is acceptable. All components of this section are intended as initial communication to introduce and alert healthcare professional of new safety information about histoplasmosis and other invasive fungal infections. It is our understanding that the communication plan is not intended to continue over the lifetime of the product.
4. We recommend incorporating the information needed to assess the effectiveness of the REMS into the approval letter.
5. The proposed patient survey protocol, methodology, and sample questions is acceptable.
6. If the Sponsor accepts the recommended changes for the healthcare provider survey, we find the survey protocol, methodology, and sample questions acceptable.
7. We recommend the Sponsor submit and note any changes in healthcare provider and patient survey protocols and sample questions to FDA 60 days prior to conducting surveys. This re-submission includes alteration of the healthcare provider survey as recommended above.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

OTHER REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: December 17, 2008
To: Administrative File, STN 125271
From: Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/MAPCB/BMT
Endorsement: Edwin Rivera, Branch Chief, CDER/OC/DMPQ/MAPCB
Subject: Memo to the BLA file: Compliance status of the manufacturing and testing facilities [redacted] (b) (4)
US License: # 1736
Applicant: UCB, Inc.
Mfg Facilities: [redacted] (b) (4)
[redacted] (b) (4)
Product: Cimzia® (certolizumab pegol 2)
Dosage: 200 mg/mL sterile solution for injection in pre-filled syringes
Indication: Treatment of rheumatoid arthritis
Due Date: December 28, 2008

Recommendation for Approvability:

1. The BLA, as amended, is recommended for approval from a CGMP compliance perspective. The compliance status of each manufacturing and testing facility listed in the BLA is acceptable and there are no pending actions that would prevent the approval of BLA 125271.
2. [redacted] (b) (4)

cGMP Status of the manufacturing and testing facilities:

The Manufacturing Assessment and Preapproval Compliance Branch completed an evaluation of the manufacturing and testing facilities listed below at the request of this reviewer. The status is as follows:

1. (b) (4)

- A district inspection was conducted on (b) (4) and included profile BTP coverage. The inspection was classified VAI and is considered acceptable.

2. UCB Manufacturing, Inc., Rochester, NY 14623 FEI 1314625; (b) (4)

- A district inspection was conducted on (b) (4) for all profiles. The inspection was classified NAI and is considered acceptable.

3. (b) (4)

- The 483 and firm's response from the recent inspection conducted by Thomas Arista in (b) (4) has been reviewed and evaluated by the International Compliance Team. The decision to classify the inspection VAI was determined based on the significance of the inspectional observations. There are no further actions to prevent approval of STN 125271/0.

4. (b) (4)

- The 483 and firm's response from the recent inspection conducted by Thomas Arista in (b) (4) has been reviewed and evaluated by the International Compliance Team. The decision to classify the inspection VAI was determined based on the significance of the inspectional observations. There are no further actions to prevent approval of STN 125271/0.

5. (b) (4)

- The 483 and firm's response from the recent inspection conducted by Thomas Arista in (b) (4) has been reviewed and evaluated by the International Compliance Team. The decision to classify the inspection VAI was determined based on the significance of the inspectional observations. There are no further actions to prevent approval of STN 125271/0.

6. (b) (4)

- No inspection information available in FACTS for assessment; however, the firm is registered as a drug manufacturer, (b) (4)

7. (b) (4)

- No inspection information available in FACTS for assessment. However, the facility was inspected in (b) (4) 6 in support o (b) (4) and Kurt Brorson (CDER/OBP/DMA) and was found to be acceptable.

Conclusion

The BLA, as amended, is recommended for approval from a CGMP compliance perspective. The no pending compliance actions that would prevent the approval of BLA 125271.

No Post marketing commitments should be communicated to the sponsor.

Cc: WO, Bldg 51, Hughes
WO, Bldg 22, Davies
WO, Bldg 51, Randazzo
WO, Bldg 51, Blue Files (STN125271)

Archived File: S:\archive\BLA\125271\STN125271.rev.mem.BLA.AD.12.17.2008.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: October 3, 2008
To: Administrative File, STN 125271
From: Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/MAPCB/BMT PFH 10/3/08
Endorsement: Edwin Rivera, Branch Chief, CDER/OC/DMPQ/MAPCB E Rivera 10/3/08
Subject: Amended review of BLA for the treatment of rheumatoid arthritis (similar application also in GI for treatment of Crohn's)
US License: # 1736
Applicant: UCB, Inc.
Mfg Facilities: (b) (4)

(b) (4)

Product: Cimzia® (certolizumab pegol 2)
Dosage: 200 mg/mL sterile solution for injection in pre-filled syringes
Indication: Treatment of rheumatoid arthritis
Due Date: 05 October 2008

Recommendation for Approvability:

The BLA, as amended, is not recommended for approval at this time. The International Compliance Team in CDER's Office of Compliance has reviewed two (b) (4) 483's issued during a recent inspection in (b) (4) and is recommending withholding approval of STN 125271 until further information (b) (4) is available for review.

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cGMP Status of the manufacturing and testing facilities:

(b) (4)

- A district inspection was conducted on (b) (4) and included profile BTP coverage. The inspection was classified VAI and is considered acceptable.

2. UCB Manufacturing, Inc., Rochester, NY 14623 FEI 1314625; (b) (4)

- A district inspection was conducted on 11/30/07 for all profiles. The inspection was classified NAI and is considered acceptable.

3. [redacted] (b) (4)

- Recent inspection findings currently under review by ICT.

4. [redacted] (b) (4)

- Recent inspection findings currently under review by ICT.

5. [redacted] (b) (4)

- Recent inspection findings currently under review by ICT.

6. [redacted] (b) (4)

- No inspection information available in FACTS for assessment.

7. [redacted] (b) (4)

- No inspection information available in FACTS for assessment.

Conclusion

The BLA is not recommended for approval. The International Compliance Team in CDER's Office of Compliance has reviewed two [redacted] (b) (4) 483's issued during a recent inspection in [redacted] (b) (4) and is recommending withholding approval of STN 125271 until further information (EIR and firm's responses) is available for review.

A request to inspect the [redacted] (b) (4) was made in [redacted] (b) (4) and remains to be completed.

The firm was requested to register the [redacted] (b) (4) and a registration number is pending.

Cc: WO, BLDG 51Hughes
WO, Bldg 22, Davies
HFD-123, Rellahan
WO, Bldg 51, Rivera
WO, Bldg 51, Blue Files (STN125271)

Archived File: S:\archive\BLA\125271\STN125271.rev.mem.BLA.AD.10.02.2008.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: October 1, 2008
To: Administrative File, STN 125271
From: Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/MAPCB/BMT PPH 10/3/08
Endorsement: Edwin Rivera, Branch Chief, CDER/OC/DMPQ/MAPCB E. Rivera 10/03/08
Kalavati Suvarna, Ph.D., Peer Reviewer, CDER/OC/DMPQ/MAPCB/BMT for KS
Subject: BLA for the treatment of rheumatoid arthritis (similar application also in GI for treatment of Crohn's)
US License: # 1736
Applicant: UCB, Inc.
Mfg Facilities: (b) (4)

(b) (4)

Product: Cimzia® (certolizumab pegol 2)
Dosage: 200 mg/mL sterile solution for injection in pre-filled syringes
Indication: Treatment of rheumatoid arthritis
Due Date: 05 October 2008

Recommendation for Approvability:

The BLA, as amended, is recommended for approval from a microbial control, sterility assurance and microbiology product quality perspective, pending satisfactory CGMP assessments of the manufacturing facilities by the International Compliance Team in the Office of Compliance.

(b) (4)

SUMMARY: This BLA was received in the Agency on 06 Dec 2007. A similar application (BLA 125260) for the same drug substance and different drug product formulation and dosage for the treatment of Crohn's disease was approved during the course of this review. Differences between the approved BLA 125260 and this BLA include a new formulation for the bulk drug substance, (b) (4) and the manufacturing process for the finished drug product. This review covers the changes in the drug substance process and the drug product

- Amendment 1, 15 February 2008 Attachment 6 – Differences in Drug Substance Manufacture between BLA 125271 and BLA 125260.
- Amendment 2, 14 March 2008: Response to Request for Information dated 29 February 2008 Comparison of the 3.2.S Drug Substance Information Presented in the Rheumatoid Arthritis (RA) BLA 125271 versus the 3.2.S drug Substance Information Presented in the Crohn's Disease (CD) BLA 125160.
- Amendment 4, dated 16 May 2008: Attachment 1- Amended page 532 – Bioburden; Attachment 2 – Amended Specification for Drug Product (3.2.P.5); Attachment 3 –

(b) (4)

(b) (4)

(b) (4)

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 23, 2008
To:	Bob A. Rappaport, M.D., Director **Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)**
Through:	Jodi Duckhorn, M.A., Team Leader 9/23/2008 **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
From:	Sharon R. Mills, BSN, RN, CCRP 9/23/2008 Patient Product Information Specialist **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
Subject:	Memo Summarizing Final Agreements on Patient Labeling (Medication Guide)
Drug Name(s):	Cimzia (certolizumab pegol)
Application Type/Number:	BLA125271
Submission Number:	0
Applicant/sponsor:	UCB, Inc.
OSE RCM #:	2008-110

SEP 24 2008

UCB, Inc. submitted a new Biologics Licensing Application, BLA 125271, on December 6, 2007 for Cimzia (certolizumab pegol), for the treatment of adults with active rheumatoid arthritis (RA). The proposed commercial formulation is a solution presented in a pre-filled syringe that is intended for self-administration by patients. With the approval of the original BLA 125160 on April 22, 2008, the sponsor's labeling submitted to BLA 125271 became inapplicable. The sponsor submitted new labeling on July 22, 2008, which combines the approved indication for Crohn's disease and information pertaining to the new proposed indication for RA. The submission includes proposed Professional Information (PI) with a proposed revised Medication Guide.

On September 17, 2008, The Patient Labeling and Education Team provided the review division with a review of the sponsor's proposed revised Medication which incorporated review division changes, dated September 11, 2008.

This memo serves to document the agreed upon changes to the Medication Guide between the review division and DRISK. We have attached the additional marked up changes to the Medication Guide using the clean copy from our September 17, 2008 as the base. Agreement to these changes between the DRISK primary reviewer and Dr. Jeffrey Siegel of DAARP took place in discussion on Friday, September 19 and in follow-up email correspondence on September 21-22, 2008. See attached.

10 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 22, 2008
To:	Kathleen Davies/ Project Manager Jeff Siegel/ Medical Officer, team leader Division of Anesthesia, Analgesia and Rheumatology Products (DAARP), HFD-170
Through	Solomon Iyasu, MD, MPH/Director Division of Epidemiology (DEPI), HFD-410 Office of Surveillance and Epidemiology (OSE)
From:	Sigal Kaplan, Ph.D, B.Pharm/Pharmacoepidemiologist Division of Epidemiology, Office of Surveillance and Epidemiology
Subject:	Review of proposed post-marketing study commitment: Registry for Rheumatoid Arthritis indication
Drug Name(s):	Cimzia® (certolizumab pegol)
Application Type/Number:	BLA # 125271/0
Applicant/sponsor:	UCB, Inc
OSE RCM #:	2008-157

EXECUTIVE SUMMARY

Cimzia® (certolizumab pegol, BLA # 125160), an anti tumor necrosis factor alpha (TNFα) agent, was approved for reducing signs and symptoms of Crohn's Disease (CD). An additional indication for rheumatoid arthritis (RA) was submitted for this product along with pharmacovigilance (PV) plan for FDA's review. The purpose of this review is to provide DEPI's comments on the PV plan for the registry and the post-marketing studies to be conducted by the sponsor following the approval of the additional indication for Cimzia®.

The PV plan proposed by the sponsor includes two additional commitments beyond the routine PV of spontaneous adverse events reporting, (b) (4) as well as participation in various disease registries for RA to further assess the risk of Cimzia®. DEPI supports both of these proposed postmarketing activities as they are consistent with the requirement for the CD indication in the approval letter for Cimzia®. Because of the voluntary nature of registries and since the FDAAA requirements are met, DEPI recommends that sponsor conduct the registries and related observational studies under as Postmarketing Requirements (PMR). Included in this review are specific DEPi recommendations for activities under the PMR.

It should be noted that the proposed registries lack sufficient details for a thorough evaluation. Detailed protocols for RA disease registries for Cimzia® and associated studies should be submitted for review.

1 INTRODUCTION

On April 22, 2008 Cimzia® (certolizumab pegol, BLA # 125160), an anti tumor necrosis factor alpha (TNFα) agent, was approved for reducing signs and symptoms of Crohn's Disease (CD) and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. A pharmacovigilance (PV) plan was submitted along with the application for FDA's review. Prior to that approval, on November 19, 2007, UCB (the sponsor) also submitted an application for Cimzia® (BLA # 125271), for the rheumatoid arthritis (RA) indication. After the approval of Cimzia® for Crohn's Disease, the sponsor submitted an amendment to the PV plan of RA indication to replace the PV plan that was submitted with the original application of RA indication, as the original PV plan for RA was submitted before the approval of Cimzia® for CD.

The Division of Epidemiology (DEPI) within the OSE was consulted to review the sponsor's revised PV plan sent on August 11, 2008. The purpose of this review is to provide DEPI's comments on the PV plan for the registry and the post-marketing studies to be conducted by the sponsor following the approval of the additional indication for Cimzia®.

2 MATERIAL REVIEWED

DEPI reviewed and commented on the following document:

- The sponsor's Integrated Pharmacovigilance Plan and Risk Minimization Activities document for RA and CD indications

As a background, DEPI reviewed the following documents:

- The sponsor's Risk Management Plan (RMP) dated November 19, 2007 for RA indication

- The sponsor's previous proposed pharmacovigilance activities for Cimzia® for CD indication

The following criteria were used to evaluate the propose registry:

- Study population (representativeness)
- Comparison group
- Sample size
- Strategies for recruitment target sample size
- Data collection contents and methods
- Follow-up time
- Safety concerns for the product
- Safety concerns for the therapeutic class

3 SPONSOR'S PROPOSED PHARMACOVIGILANCE PLAN

3.1 SUBMISSION OF SPECIFIC SERIOUS ADVERSE EVENT REPORTS

In addition to routine pharmacovigilance reporting required by the regulation (21 CFR 600.80), UCB commits to report the following adverse event reports for both indications (CD and RA) as

(b) (4)

3.2 CIMZIA® REGISTRIES

3.2.1 Crohn's Disease

UCB has committed to conduct a long-term observational study in the U.S. that will include approximately 2000 Cimzia®-treated CD patients and 2000 matched controls receiving other treatments for CD. Patients will be followed for 10 years. The sponsor committed to submit the final study protocol for FDA's comment by September 1, 2008.

3.2.2 Rheumatoid Arthritis

The sponsor states that they commit to adding Cimzia® to existing U.S. and European post-marketing registries and participate in the following Registries:

In the U.S.

- *National Databank (NDB) for Rheumatic Diseases.* The objective of the sponsor 's participation in this registry is to develop a study that would detect a two-fold increase in the risk of serious infection, lymphoma, and solid malignancies (defined as excluding lymphoma and non-melanoma skin cancer). It is estimated that the required sample population will be about 5,000 Cimzia®-treated patients and 7,500 non-biologic-treated controls and the evaluation duration will be about 6 years.
- *The Organization of Teratology Information Specialists (OTIS)*

(b) (4)

(b) (4)

4 DEPI'S COMMENTS

It is worth noting that the sponsor has mentioned a safety concern from non-clinical studies on (b) (4) Though the applicability of these finding is unknown for humans and may be associated with the disease for which the drug is taken, it may be worth following up this risk. DEPI discussed safety concerns with safety evaluators in the Division of Pharmacovigilance within OSE to verify that no new signals or safety concerns have been identified since the time the product was approved (April 2008).

The PV plan proposed by the sponsor includes (b) (4) for the RA indication are acceptable, as they are consistent with the requirement for the CD indication in the approval letter for Cimzia®. Therefore these (b) (4) will be required for Cimzia® product, regardless of the indication for which the product was prescribed.

The second commitment includes participation in various disease registries for RA to further assess the risk of Cimzia® in comparison to other products in the market. DEPI has determined that the sponsor's proposal to participate in such disease registries for RA and conduct long term observational study should be required. Cimzia®, as a member of the TNF blocker class, has been associated with known serious risks of serious infections, including opportunistic infections, development of lymphoma and other malignancies, and development of demyelinating disorders. While Post marketing open label studies are required for Cimzia® and may provide additional data on the safety issues associated with this product, an analysis of spontaneous postmarketing adverse events reported will not be sufficient to assess these known serious risks or to identify unexpected serious risks. Furthermore, a new pharmacovigilance system, such as active surveillance, has not yet been established to assess these known or unexpected serious risks.

Therefore, the use of registries with large number of patients followed for long-term period may identify safety issues that are more likely to be detected during long-term follow-up period rather during short-term postmarking clinical trials. Moreover, it allows consistency across previous requirements for registries within product (PMRs have been required for CD indication) and across other TNF blocker products.

However, the proposed additional PV activities lack sufficient details for a thorough evaluation. Detailed protocols for the Cimzia® registry and its associated studies should be submitted for review. We offer the following preliminary comments for the Sponsor's consideration. These comments are similar to the comments we sent to the sponsor on their proposal for Cimzia® registry for CD.

- Registry is usually voluntary and consists of an organized collection of uniform data on patient populations defined by a particular disease, outcome or exposure. Such registries could be used as data source from which observational or other studies can be conducted. It could be used to generate and test hypothesis as well as be used to assess risk if it is designed as a population-based registry study with a pre-specified hypothesis, data collection, analytic plan and an appropriate comparison group consisting of patients receiving other treatments. The objective for encouraging CIMZIA-treated patients to participate in a registry is to provide a patient population for a study that would detect a pre-specified increase in the risk of serious adverse events of interest.
- Patients enrolled in the registries and those selected for subsequent studies should be representative of clinical settings in which the drug would be given and representative of the patient population to whom the drug would be given (e.g., children).
- Although the number of potential participants is provided, there is no justification on where these figures came from or why they were chosen. The sample size proposed may not be sufficient for detecting less common events such as cancers unless the relative risk is substantially increased. The Sponsor should provide the power/sample size calculations for a range of relative risks, based on the background incidence rates of the specific events of interest. Also, strategies to ensure successful recruitment and participation of the target sample size should be provided.
- The sponsor should provide a complete description of the existing registries and specify what safety issues these registry based studies will identify. In the proposal, the sponsor should state a prespecified hypothesis, analytic approach, appropriate control, complete and appropriate follow-up, and ascertainment of outcomes for the study based on the data from the population based registry. We were able to find the following websites for some of the registries mentioned in the sponsor's proposal:
    - National Databank (NDB) for Rheumatic Diseases
      http://www.arthritis-research.org/
    - The Organization of Teratology Information Specialists (OTIS)
      http://www.otispregnancy.org/otis_registries.asp
    - [redacted] (b) (4)

  Moreover, the sponsor suggests that they will participate in the RA registries. However, they should describe how successful these registries are in recruiting patients, what does participation in the existing registries means for their drug, and how this participation will fulfill the objectives of the PV plan to detect increased risk of adverse events. It is unclear if all the safety concerns with Cimzia® as delineated below will be addressed by the registries mentioned.
    - Infections such as tuberculosis and serious opportunistic infections
    - Lymphoma and malignancies
    - Hypersensitivity
    - Autoimmune disorders
    - Neurological events and demyelination-like disorders
    - Congestive heart failure
    - Hematological disorders
    - Hepatological disorders
    - Dermatological disorders

- The sponsor should provide a description of comparison/control group for each of the registry based studies they plan to conduct
- The sponsor should provide a strategy of how they will ascertain adverse events through active surveillance: for example, through contact with patient's physicians, patient notification toll-free numbers to contact the registry when an event occurs, searching the National Death Index for all deaths and searching state cancer registries etc. It is not enough to rely on passive surveillance of participants.
- The sponsor should provide a strategy of how special populations, such as pregnant women, children, and elderly), not studied in the clinical trials, will be identified and evaluated if prescribed Cimzia® and how their risk will be assessed.
- The duration of follow-up proposed by the Sponsor (b) (4) may be acceptable to detect infection but is insufficient to detect certain malignancies with a long latency. Follow-up should be lengthened from (b) (4) years per subject to capture a more complete spectrum of malignancies.
- The sponsor should provide a plan for data collection and how they plan to capture important clinical attributes at baseline and follow-up, including:
  - (b) (4)

With regard to the Sponsor's risk minimization activities. Cimzia® was approved on April 22, 2008 with a Risk Evaluation and Mitigation Strategy (REMS) that includes a Medication Guide and a timetable for assessment. The Agency plans to request a modification to the REMS to include a communication plan to healthcare providers regarding the risk of histoplasmosis.

5 CONCLUSIONS AND RECOMMENDATIONS

(b) (4)

DEPI also supports the sponsor's proposal to use registries as a means to collect safety data on anti-TNF exposed population and non anti-TNF exposed population. DEPI believes an analysis of spontaneous postmarketing adverse events reported will not be sufficient to assess these known serious risks or to identify unexpected serious risks. Furthermore, a new pharmacovigilance system, such as active surveillance, has not yet been established to assess these known or unexpected serious risks. In addition to the important information that can be collected in such setting, the use of registries provides consistency within the product and across other TNF blocker products. Most of the safety information up to date on Cimzia is collected through clinical trials and more safety issues might be detected during long-term follow-up. Because of the voluntary nature of registries and since the FDAAA requirements are met, DEPI recommends that sponsor conduct the registries and related observational studies under a PMR.

The sponsor has not yet submitted a detailed protocol for the Cimzia® registry and related studies. Therefore, DEPI's comments refer to the proposed conceptual contents and the substance

of registry protocol and the sample size of the related observational studies. The proposed additional PV activities lack sufficient detail for a thorough evaluation. Detailed protocols for the Cimzia® registry and the related observational studies should be submitted for review.

Sigal Kaplan, Ph.D, B.Pharm
Epidemiologist
Division of Epidemiology (DEPI)

Concurrence:
Tarek Hammad, MD, PhD, MSc, MS
Acting Team Leader
Division of Epidemiology (DEPI)

Solomon Iyasu, M.D., M.P.H.
Acting Director
Division of Epidemiology (DEPI)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 18, 2008

TO: Kathleen Davies, Regulatory Health Project Manager
Carolyn Yancey, M.D., Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Drug Products

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125271

APPLICANT: UCB Inc.

DRUG: Cimza (certoluzimab pegol)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Adult patients with active rheumatoid arthritis.

CONSULTATION REQUEST DATE: February 27, 2008

DIVISION ACTION GOAL DATE: August 5, 2008

PDUFA DATE: October 5, 2008

I BACKGROUND:

The review division requested inspection of protocol CDP870-027 entitled: "A phase III multi-center, double-blind, placebo-controlled, parallel group 52-week study to assess the efficacy and safety of 2 dose regimens of lypholilised CDP870 given subcutaneously as additional medication to methotrexate in the treatment of signs and symptoms and preventing structural damage in patients with active rheumatoid arthritis who have an incomplete response to methotrexate"; and protocol CDP670-050 entitled: "A phase III multicenter, double-blind, placebo-controlled, parallel group 24-week study to assess the efficacy and safety of two dose regimens of liquid certolizumab pegol as additional medication to methotrexate of signs and symptoms of rheumatoid arthritis and in the prevention of joint damage in patients with active rheumatoid arthritis who have an incomplete response to methotrexate". The sponsor submitted results from these two protocols in support of BLA 125271.

The primary objective of the study protocol CDP870-027 was to assess the efficacy and safety of two dose regimens of CDP870 in combination with methotrexate (MTX) compared MTX alone in the treatment of signs and symptoms in patients with active rheumatoid arthritis (RA), and in the prevention of structural damage inpatients with RA, and another objective was to assess the pharmacokinetics profile and immunogenicity of the two dose regimens. For study CDP870-050 the primary objective was to compare the efficacy of two does regimens of liquid formulation of certolizumab pegol in combination with MTX to MTX alone in the treating the signs and symptoms of patients with active rheumatoid arthritis. The inspections targeted two foreign clinical investigators who enrolled a relatively large number of subjects. The goals of the inspection included validation of submitted data and compliance of study activities with FDA regulations. The records inspected included, but were not limited to, 100% informed consent forms, source documents, drug accountability records, protocol inclusion/exclusion criteria, randomization procedures, efficacy end points and documentation of adverse events. In addition, the sponsor was inspected because this is a new molecular entity.

II. RESULTS (by protocol/site):

Name of CI, site #and location	Protocol # of subjects	Inspection Dates	Final Classification
Dagmar Micekova, M.D. 921 01 Piestany Slovak Republic Site #122	CDP870-027 24	6/2-6/08	NAI
Galina Matsievskaia, M.D. St. Petersburg 190068 Russia Site# 111 and 154	CDP870-027 & CDP870-050 28 & 30	5/26-30/08 6/9-12/08	NAI

UCB, INC.	Same as above	6//08	Pending preliminary classification:NAI

Key to Classifications
NAI = No deviation from regulations
VAI = deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol CDP870-027

1. Damgar Micekova, M.D.
   National Institute of Rheumatoid Disease
   Nabbrezie I, Krasku 4
   921 01 Piestany
   Slovak Republic

   At this site a total of 27 subjects were screened, 24 subjects were enrolled in the study, 3 subjects were reported as screen failures but continued on the study, and four subjects were discontinued due to lack of efficacy. Nineteen subjects completed the study and only subject 122026 was discontinued due to persistent pain and swelling and methotrexate dose was suspended due to hepatic toxicity. The records for all subjects were verified to have signed informed consent prior to entry into the study. The medical records for 12 subjects were reviewed in depth and compared source documents to case report forms and data listings for primary efficacy end points and adverse events. No adverse events were noted, and no deaths.

   The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. The limitation for this inspection is a language barrier (Slovak).

   The data appear acceptable in support of the pending application.

   Note: None of the visual analogue scale (VAS) measurements for global assessments of pain and disease activity reported in the case forms and data listings could be verified since the VAS measurements provided in the case report forms (CRFs) and the data listings were done by the sponsor. The CRFs did not provide a space to document the measurements. The sponsor eventually provided the site with a transparent ruler and directed the investigator to measure the assessments and document the information in the CRFs. The clinical investigator and the subject were requested to initial and date their completed assessments. The investigator's and subjects' measurements were sent to the sponsor's data management group, which then did its own measurement of the visual analogue scales. The sponsor reportedly included both sets of measurements in the trial database but provided only the sponsor's measurements in the data listings, reportedly because the sponsor considered its own measurements more accurate because there was less variance in measuring technique.

   In addition, some Health Assessment Questionnaires (HAQs) were not completed at the screening visits for certain subjects. Dr. Micekova stated that this was due to a delay initially in receiving the HAQ forms.

As noted, the sponsor calculated all of the VAS measurements in the CRFs and data listings. As a result, we were unable to verify these data at this inspection. The remaining data that were verifiable appear acceptable in support of the application.

Protocols CDP870-027 and CDP870-050

2. Galina K. Matsievskaia, M.D.
City Hospital #25(City Rheumatology Ctr)
B Pod'yacheskaya, 30
St. Petersburg 190068
Russia

Protocol CDP870-027: At this site, a total of 30 subjects were screened, 2subjects were reported as screen failure, 28 subjects were enrolled, 23 subjects completed the study and 5 subjects withdrew from the study due to lack of efficacy. The records for all subjects were verified to have signed informed consents prior to screening and randomization into the study. The medical records for 11 subjects enrolled were reviewed in depth including drug accountability records and compared source documents to case report forms and data listings for primary efficacy endpoint and adverse events. Adverse events experienced by study subjects (111002 experienced allergic dermatitis; 111018 experienced allergic reaction; 111019 had a fractured right elbow; and 111024 had fever) were accurately reported to the sponsor and the IRB.

Protocol CDP870-050: At this site, a total of 31 subjects were screened, one subject with positive PPD test was reported as screen failure, 30 subjects were enrolled, 15 subjects completed the study, 14 subjects withdrew from the study due to lack of efficacy, and one subject withdrew due to serious adverse event (fever). The records for all subjects were verified to have signed informed consents prior to screening and randomization into the study. The medical records for 14 subjects enrolled were reviewed in depth including drug accountability records and compared source documents to case report forms and data listings and adverse events. Adverse events experienced by study subjects (1540004 had an eye procedure which required hospitalization; 1540006 had infiltrative tuberculosis; and 1540012 experienced menorrhagia and was hospitalized) were accurately reported to the sponsor and the IRB.

The medical records reviewed for both protocols disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. The limitation to this is a language (Russian).

The data from both protocols appear acceptable in support of the pending application.

Note: None of the visual analogue scale VAS measurements for global assessments of pain and disease activity reported in the case report forms and data listings could be verified since the VAS measuements provided in the case report forms (CRFs) and the

data listings were done by the sponsor. The case report forms did not provide a space to document the measurements and the clinical investigators did not complete the pain scores and global assessments. As a result, the sponsor directed the investigators to measure the assessments and document the information in the case report forms. The clinical investigators and the subjects were requested to initial and date their completed assessments. The investigator's and subject's measurements were sent to the sponsor's data management group, which then did its own measurement of visual analogue scales. The sponsor reportedly included both sets of measurements in the trial database but provided only the sponsor's measurements in the data listings, reportedly because the sponsor considered its own measurements more accurate because there was less variance in the measuring technique.

In addition, some Health Assessment Questioneres (HAQs) were not completed at the screening visits for certain subjects.Dr. Matseivskaia stated that this was done due to a delay initially in receiving tha HAQ forms.

As noted, the sponsor calculated all of the VAS measurements in the CRFs and data listings. As a result, we were unable to verify these data at this inspection. The remaining data that were verifiable appear acceptable in support of the application.

3. UCB, Inc.
1950 Lake Park drive
Smyrna, Georgia 30080

Celltech was the original sponsor of the above studies CPD 870-027 and 050. A merger between Celltech and UCB was reported as December 28, 2005.

The study activities of the sponsor, UCB, Inc contracted with (b) (4) was contracted to perform the radiograph x-rays for both studies. X-rays of the hands and feet were used to assess the inhibition of structural damage progression. The x-rays were taken prior to treatment at baseline and at weeks 24 and 52/withdrawal. The degree of joint damage was assessed using the Total Sharp Score (mTSS) that quantifies the extent of bone erosions and joint space narrowing. Each x-ray was read centrally by 2 of 3 readers who were blinded to the trial treatment and patient identification. The mean score of the readers was used for analyses. UCB audited (b) (4) and identified problems with data transmission. UCB corrected the deficiencies and submitted the information to FDA. The review division is aware of the summary report.

The monitoring activities of the sponsor, UCB, Inc. were reviewed during the inspection. The trial files for the study sites' protocols were reviewed, including SOPs, outside services/contractors, the written agreements, IRB records, completed Form FDA 1572s, investigators qualifications, monitoring and staff qualifications, non-

compliant sites, study records, how adverse events were reported and drug accountability records.

Review of the records noted above revealed no significant discrepancies/regulatory violations. Data generated from above sites appear acceptable in support of the respective application

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

There was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication and had their primary efficacy endpoint captured as specified in the protocol. Overall, the inspection of Drs. Micekova and Matsievskaia revealed that the VAS measurements were not available at the respective sites and therefore, we were not able to verify these data at the two sites. The remaining data generated and submitted from the inspected sites are acceptable in support of the pending application. The sponsor's monitoring procedures appears to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective application.

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

Constance Lewin, MD, MPH

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 17, 2008
To:	Bob A. Rappaport, M.D., Director **Division of Analgesics, Anesthetics and Rheumatology Products**
Through:	Jodi Duckhorn, M.A., Team Leader Jduckhorn 9/17/2008 **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
From:	Sharon R. Mills, BSN, RN, CCRP Sharon R. Mills 9/17/2008 Patient Product Information Specialist **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
Subject:	Review of Patient Labeling (Medication Guide with Patient Instructions for Use)
Drug Name(s):	Cimzia (certolizumab pegol)
Application Type/Number:	BLA 125271
Submission Number:	0
Applicant/sponsor:	UCB, Inc.
OSE RCM #:	2008-110

1 INTRODUCTION

UCB Inc's original Biologics Licensing Application, BLA 125160, was approved on April 22, 2008, for Cimzia (certolizumab pegol), indicated for reducing the signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. Cimzia is currently available as a lyophilized powder for reconstitution with sterile Water for Injection, USP, and is administered by a healthcare provider. Cimzia is a member of the class of tumor necrosis factor (TNF) –blockers. Because of the similar safety concerns as with other members of this class that Cimzia poses a serious and significant public health concern due to the risk of serious infections, Cimzia was approved with a Medication Guide.

UCB, Inc. submitted a new Biologics Licensing Application, BLA 125271, on December 6, 2007 for Cimzia (certolizumab pegol), for the treatment of adults with active rheumatoid arthritis (RA). The proposed commercial formulation is a solution presented in a pre-filled syringe that is intended for self-administration by patients. With the approval of the original BLA 125160 on April 22, 2008, the sponsor's labeling submitted to BLA 125271 became inapplicable. The sponsor submitted new labeling on July 22, 2008, which combines the approved indication for Crohn's disease and information pertaining to the new proposed indication for RA. The submission includes proposed Professional Information (PI) with a proposed revised Medication Guide.

This review is written in response to the review division for the Patient Labeling and Education Team to review the sponsor's revised proposed Medication Guide (MG) with Patient Instructions for Use. The review division has not provided revisions at the time of our review.

2 MATERIAL REVIEWED

- DRAFT CIMZIA (certolizumab pegol) Professional Information (PI) submitted by the sponsor on July 22, 2008 and further revised by the review division on September 11, 2008.
- DRAFT CIMZIA (certolizumab pegol) Medication Guide (MG) with Patient Instructions for Use submitted by the sponsor on July 22, 2008, and further revised by the review division on September 11, 2008.

3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the sponsor has a Flesch Kinkaid grade level of 7.8, and a Flesch Reading Ease score of 62.4%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the sponsor are acceptable. In our review of the MG, we have:

- simplified wording and clarified concepts where possible,

- ensured that the MG with Patient Instructions for Use is consistent with the PI,
- rearranged information due to conversion of the PI to PLR format,
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG with Patient Instructions for Use meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG with Patient Instructions for Use document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG with Patient Instructions for Use. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG with Patient Instructions for Use. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG and Patient Instructions for Use.

4 CONCLUSIONS AND RECOMMENDATIONS

1. The sponsor proposes that patients who are prescribed Cimzia in the Prefilled Syringe formulation will be permitted to self-administer the product. The sponsor should state their planned mechanism for ensuring that all patients who are prescribed CIMZIA, especially patients prescribed the Cimzia Prefilled Syringe, receive the MG. The Patient Instructions for Use which are being added to the MG with this BLA are important for safe use of the product by patients (self-administration).
2. In section 2.2 of the PI, the review division has added language regarding RA, that "CIMZIA should not be used in combination with biological disease modifying antirheumatic drugs (biological DMARDs) or other tumor necrosis factor (TNF) blocker therapy." Section 2.6 Concomitant Medications states that "CIMZIA may be used as monotherapy or concomitantly with non-biologic DMARDs. We have added the following language to the MG section "What is CIMZIA?" to reflect this information:

   > "You should not receive CIMZIA for RA along with a biologic disease modifying antirheumatic drug (biologic DMARDs) or other TNF blocker medicines. Your risk of serious infection may be higher. CIMZIA may be used alone or with a DMARD that is not a biologic. Ask your doctor if you are not sure if your medicine is a biologic DMARD or TNF blocker."

3. PI section 11 Description states that "CIMZIA is a clear to opalescent solution that is colorless to pale yellow [redacted] (b) (4)

The sponsor should further clarify this for patients and determine if [redacted] adequately describes what patients should look for.

4. In the section "What are the possible side effects of Cimzia?" :

   - We added the following statement to the bullet for heart failure:

     "Increased chance of death from heart failure has been seen with another TNF blocker medicine."

     Add information about fast weight gain as a possible symptom of heart failure.

   - Hepatitis B reactivation is included as [redacted] Warnings and Precautions. As with the other TNF blocker MGs, the CIMZIA MG should address this. We have added the language from the currently approved HUMIRA MG.

   - Injection site reactions are listed in the currently approved MG. Describe the injection site reaction in the PI and in the MG. Provide an instruction about any reportable signs or symptoms.

   - Under the bullet for allergic reactions: Angioedema can cause swelling of the tongue, lips, throat, not just the face. Add these symptoms.

   - The RD should clarify the percentage cutoff used in listing adverse reactions in the MG. We note that section 6.1 of the PI for RA includes among the most common adverse events occurring at a higher percentage than placebo treated patients in the placebo-controlled trials: upper respiratory tract infections, [redacted]

     Additionally, the PI describes the most common adverse reactions in premarketing controlled trials of all patient populations combined as upper respiratory infection, rash and urinary tract infection. These are the three adverse reactions currently listed in the MG (as revised by the review division) as being common with CIMZIA. Clarify whether language should be added to the PI related to common adverse events in Crohn's disease for parity. Otherwise, it is difficult for the reviewer to determine how to separate out the side effects by patient population in the MG. We have added lower respiratory tract and lung infections for RA patients. Clarify how "bacterial infections" should be explained in the MG for RA patients given the other references to infections.

5. In the section "How should I store CIMZIA?" [redacted]

6. In the Patient Instructions for Use, the sponsor should add a labeled figure for each step and reference each as appropriate in the text. Also add a labeled figure showing all of the needed supplies to prepare and give an injection, including the puncture-proof disposable container.

Please let us know if you have any questions.

22 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Cc List:

Division of Analgesics, Anesthetics and Rheumatology Products
Bob A. Rappaport
Carolyn Yancey
Kathleen Davies

OSE/Division of Risk Management
Claudia Karwoski
Mary Dempsey
Jodi Duckhorn
Sharon Mills
Nancy Carothers

OSE/Review Management Staff
Chris Wheeler

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: **09/11/2008**

To: Kathleen Davies - Regulatory Project Manager
Division of Anesthetics, Analgesics, and Rheumatology Products (DAARP)

From: Mathilda Fienkeng PharmD - Senior Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: BLA 125160
DDMAC labeling comments for Cimzia (certolizumab pegol) lyophilized powder for solution and solution for subcutaneous injection

---

DDMAC has reviewed the proposed PI, proposed carton and container labeling for CIMZIA and offer the following comments:

HIGHLIGHTS

Indication and Usage:

1. " . . . treatment of adults with moderately to severely active rheumatoid arthritis"

   Please consider revising this to reflect the efficacy end point of its use (limitations) and to be consistent with the labeling language in other TNF blockers used for RA as follows:

   "Cimzia is indicated for reducing the signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis."

Warnings and Precautions:

1. "cases of lymphoma and other malignancies have been observed among patients receiving TNF blockers"

We recommend revising the above as follows for consistency with the Cimzia PI and labeling language in other TNF blockers:

"Malignancies – cases of lymphoma and other malignancies have occurred among patients receiving TNF blockers including Cimzia"

FULL PRESCRIBING INFORMATION

Indication and Usage:

1. " CIMZIA is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis (RA)"

Please consider revising the indication as mentioned in first comment and also consider moving pertinent information from current section 2.6 to section 2.2 to improve clarity, material facts to usage of Cimzia for RA indication as well as consistency with PI for other TNF blockers as follows

"Cimzia is indicated for reducing the signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. Cimzia can be used as monotherapy or concomitantly with non-biologic DMARDs."

Dosage and administration:

1. Section 2.2,

If the 200mg dose should be given with MTX, consider revising the dosage to specify.

If the 400mg can not be given with concomitant MTX, consider including this in section 2.2

Warnings and Precautions:

(b) (4)

1. "An increased risk of serious infections has been seen in clinical studies with other TNF blocking agents . . ."

As proposed, "an increased risk" suggests that a potential increase risk rather than actual serious infections were seen in clinical studies. We recommend revising this to

"Serious infections were seen in clinical studies with other TNF blocking agents. . ."

6.1 Clinical trials experience

1. As proposed, the adverse reactions are presented after *". . . because clinical studies are conducted under widely varying . . .",* this decreases the prominence of the adverse reactions being reported and is not consistent with current labeling of other TNF blockers for same indication.

Please consider moving this paragraph to the end of the paragraph presenting Adverse reactions in all Premarketing Controlled Trials Combined. (Before the section titled "Infections")

2. Tuberculosis and Opportunistic Infections:

"No cases of TB have been reported in the US or Canada across all indications"

This statement minimizes the seriousness of this risk and we recommend that it be deleted.

Drug Interactions:

7.1 Use with Anakinra and Abatacept (same as previous comment under warning section)

"an increased risk of serious infections has been seen in clinical studies with other TNF blocking agents . . ."

We recommend revising this to state

"Serious infections were seen in clinical studies with other TNF blocking agents. . ."

Medication Guide:

Under section **"What is Cimzia?"** consider revising the language related to indication for RA (see first recommendation).

For Section: **What are the possible side effects of CIMZIA?**

Consider including the following for consistency with the highlights and warning sections of the PI and the PI for the other TNF blockers:

"Hepatitis B virus reactivation inpatients who carry the virus in their blood. In some cases patients have died as a result of hepatitis B virus being reactivated. Your doctor should monitor you carefully during treatment with Cimzia if you carry the hepatitis B virus in your blood. Tell your doctor if you have any of the following symptoms:

- *Feel unwell*
- *Poor appetite*
- *Tiredness (fatigue)*
- *Fever, skin rash, or joint pain.*

Thank you for the opportunity to comment on this label.

Mathilda Fienkeng 9/11/08

Mathilda Fienkeng PharmD
DDMAC Reviewer
301 796 3692

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 10, 2008
To:	Bob Rappaport, MD, Director Division of Anesthesia, Analgesia and Rheumatology Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Kellie Taylor 9/10/08 Denise P. Toyer, PharmD, Deputy Director DPToyer 9/10/08 Carol Holquist, RPh, Director CHolquist 9/11/08 Division of Medication Error Prevention and Analysis (HFD-420)
From:	Laura Pincock, RPh, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (HFD-420)
Subject:	Label and Labeling Review
Drug Name(s):	Cimzia (certolizumab pegol) Injection 200 mg per mL pre-filled syringes
Application Type/Number:	BLA 125271/0
Applicant/sponsor:	UCB, Inc.
OSE RCM #:	2008-105

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed carton labeling and container labels is vulnerable to confusion that could lead to medication errors. Specifically, the concerns surround the readability and communication of information on the syringe label, carton labeling, prescribing information labeling, and Medication Guide. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.2 INTRODUCTION

This review was written in response to a request from the Office of Anesthesia, Analgesia and Rheumatology, for assessment of the proposed container labels and carton labeling for Cimzia Injection.

We previously reviewed the proprietary name, Cimzia, and the container labels and carton labeling for Cimzia lyophilized powder for injection (BLA 125160) in OSE Review # 2008-458, dated April 3, 2008. The Cimzia lyophilized powder for injection was approved on April 22, 2008 for the treatment of Crohn's Disease. The Cimzia pre-filled syringes are proposed for the treatment of Rheumatoid Arthritis and will be discussed in this review.

OSE participated in a telephone conference with the Applicant and OND/DAARP on August 18, 2008. At that teleconference, the Applicant stated their intention to market both the lyophilized powder and the pre-filled syringes indefinitely. Eventually, they hope to have each dosage form approved for both indications of use.

1.3 PRODUCT INFORMATION

Cimzia (certolizumab pegol) injection is a tumor necrosis factor proposed to be indicated for treatment of adults with active rheumatoid arthritis. The recommended adult dose of Cimzia is 400 mg given as two subcutaneous injections of 200 mg initially and at weeks 2 and 4, followed by 200 mg every other week. An alternative dosing schedule of Cimzia 400 mg every four weeks can be considered as a maintenance dose. Cimzia is intended for use under the guidance and supervision of a physician. A patient may self-inject Cimzia if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.

Cimzia will be supplied in a carton containing:

1. 2 single use pre-filled glass syringes with fixed needles of Cimzia injection, 200 mg per mL
2. Full Prescribing Information with approved Medication Guide
3. 2 alcohol preps

Patients will need to supply their own cotton ball or gauze pad. Cimzia syringes should be stored in the refrigerator at 2 to 8°C. However, Cimzia should be brought to room temperature before injection.

2 METHODS AND MATERIALS

This section describes the methods and materials used by medication error staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event

that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton labeling and container labels communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because the Division of Medication Error Prevention and Analysis staff analyze reported misuse of drugs, the staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The Division of Medication Error Prevention and Analysis uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on December 6, 2007 and August 20, 2008, the following container labels and carton labeling for the Division of Medication Error Prevention and Analysis review (see Appendices A and B for images):

- Syringe Labels (retail and sample): 200 mg per mL (each pre-filled syringe contains 1 mL)
- Carton Labeling (retail and sample): each carton contains two single dose prefilled syringes and supplies
- Prescribing Information Labeling (no image)
- Medication Guide (no image)
- Oxo-Grip Syringes (no image)
- Proposed changes to the Cimzia Cimplicity Distribution Program and Specialty Pharmacy Network (no image)

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

Review of the container label and carton labeling identified several potential sources of medication error. Specifically, important information must be clearly conveyed with respect to prominence of the proprietary name, established name, strength, and net quantity.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3.1 General Comments

The Review Division and Applicant state that the two dosage formulations of Cimzia will co-exist in the marketplace for some time, initially with one dosage form (lyophilized powder) approved for the treatment of Crohn's Disease and the second dosage form (pre-filled syringes) approved for the treatment of Rheumatoid Arthritis.

The Cimzia product for Crohn's disease (lyophilized powder) is currently approved. The lyophilized powder vials must be reconstituted and prepared for administration, which requires knowledge and training to prepare and administer the dose correctly. The applicant did not assess patient self-administration in clinical studies, thus the insert labeling for Cimzia states the lyophilized powder should be prepared and administered by a healthcare professional. However, the new dosage form (the pre-filled syringes) does not require reconstitution and the updated insert labeling states that "a patient may self-inject Cimzia if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique." Thus, there is a difference between the two products' recommendations as to who may administer the dose.

Each carton contains the same net quantity of Cimzia [two dosage units (vials or syringes) to administer a 400 mg dose]. The cartons for each product do not convey the particular indication for which it is approved. DMEPA is concerned that the end recipient of the product (patient or healthcare professional) may not get the intended dosage form, and that patients may try to mix the lyophilized powder dosage form.

3.2 Syringe Label

The strength (e.g., 200 mg/mL) is printed in very small and colored font making it difficult to read.

The syringe label does not clearly identify the space for the lot number and expiration date for the product.

The syringe label lacks a statement on the principal display panel regarding the net quantity of product (e.g., 1 mL) contained in each syringe.

3.3 Carton Labeling

The carton labeling lacks a statement that each syringe is intended for a single use and that any remaining product in the syringe should be discarded after a single use.

The carton labeling lacks a statement on the principal display panel regarding the net quantity of product (e.g., 1 mL) contained in each syringe.

The carton labeling contains the statement "no US standard of potency".

The principal display panel of the carton labeling contains the promotional statement "Syringe designed in partnership with OXO Good Grip" (with logo).

3.4 Prescribing Information Labeling

The Dosage and Administration section of the Highlights of Prescribing Information is not consistent with the Dosage and Administration section under the Full Prescribing Information. Specifically, the text in the Highlights of Prescribing Information does not convey that the 400 mg dose is comprised of two subcutaneous injections of 200 mg.

3.5 Medication Guide

The Medication Guide does not clearly state that two syringes of 200 mg must be administered to comprise a dose of 400 mg.

The Medication Guide does not contain a warning to patients and healthcare providers that they should not attempt to place the needle cover back on the syringe or otherwise recap the needle.

3.6 Prefilled Syringes

The prefilled syringes are calibrated and contain a clear label overtop making it difficult to read the calibrations and the print on the label.

4 DISCUSSION

Our analysis of the proposed labels and labeling identified areas of vulnerability such as the poor readability of text on the container label and carton labeling, and a lack of information that could impact the safe use of the product.

4.1 General Comments

DMEPA is concerned that two dosage formulations of Cimzia will co-exist in the marketplace, because this introduces the potential for confusion between the two products. We note that the newest versions of the insert labeling are combined to make one version that includes both dosage forms which raises concern because one formulation is intended for administration by a healthcare practitioner only while the other may be administered by the patient.

The Cimzia product for Crohn's disease (lyophilized powder) is currently approved for healthcare professional administration only. The lyophilized powder vials must be reconstituted and prepared for administration, which requires knowledge and training to prepare and administer the dose correctly. Thus, the insert labeling for the lyophilized powder states that Cimzia should be prepared and administered by a healthcare professional. However, the new dosage form (the pre-filled syringes) does not require reconstitution and the insert labeling states that "a patient may self-inject Cimzia if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique." Thus, there is a difference between the two products' recommendations as to who may administer the dose.

This difference could be problematic, because both products could be stocked in a pharmacy for dispensing to patients. It is not apparent, when looking at the outside cartons of each product, which product is intended for which indication. Each carton contains two dosage units (vials or pre-filled syringes) of 200 mg to provide a 400 mg dose so the net milligram contents of each carton are identical. A pharmacist may not know that the lyophilized powder is intended for Crohn's Disease and health care professional administration only; whereas the pre-filled syringes are intended for Rheumatoid Arthritis and may be administered by either a healthcare professional or the patient. Furthermore, because the initial dosing regimens are the same, it is not likely the pharmacist will know or be able to determine from a prescription whether the patient has Rheumatoid Arthritis or Crohn's Disease and thus which dosage form they should dispense. Therefore, it is possible for the patient to receive the product that corresponds to the other indication and not understand how to prepare the medication for administration.

Clinically, this may not be significant because the patient will receive the correct milligram dose of Cimzia (400 mg) as long as the product is mixed and administered correctly. However, if a patient has been trained to use the pre-filled syringes, but then receives the lyophilized powder vials when the prescription is filled, they may not be able to correctly reconstitute the powder which may lead to a dosing or administration error. The lyophilized powder is not intended for patient self-administration, so its Medication Guide was not written with patient friendly instructions for reconstitution of the lyophilized powder. Patients may misinterpret or not follow the instructions and administer an incorrect or incorrectly prepared dose which could cause harm.

We presented these concerns in an August 18, 2008 teleconference between OSE, the Applicant and the Review Division. Since this teleconference the Applicant has proposed changing the current Cimplicity Distribution Program and Specialty Pharmacy Network to ensure that distribution of the prefilled syringes is the default option. The proposed changes are as follows:

- Prescriptions submitted to the specialty pharmacy through Cimplicity will be asked to specify the liquid prefilled syringes or lyophilized product.

- The UCB Cimplicity Patient Referral Form will be altered to reflect this option. If this is inadvertently left blank, the service center will contact the physician to obtain the necessary information.

- Wholesalers will be stocked by UCB Cimplicity specialty pharmacies with liquid prefilled syringes only, thereby limiting access to liquid prefilled syringes only as the default option.
    - Lyophilized product will be available from the UCB specialty pharmacies to wholesale/retail channels only upon specific request.

As a result, it is anticipated these proposed measures will limit access to the lyophilized powder, so that the prefilled syringes are the default dosage form to be dispensed from pharmacies. This should reduce the potential for the patient to be dispensed the wrong dosage form. DMEPA finds this proposal acceptable as an adequate approach to manage the risk of dosage form confusion.

4.2 Syringe Label

The strength on the syringe label (e.g., 200 mg/mL) is printed in very small colored font making it difficult to read. The syringe label submitted for our review also features the strength printed in bright green ink which further decreases the readability. DMEPA maintains that the strength must be prominent and legible because it is important for the user to readily determine the contents in the syringe, particularly since two syringes must be administered to achieve the recommended dose of 400 mg.

DMEPA notes that there is not a clearly identified space on the syringe label for the lot number and expiration date. We note that there is white space with the letters 'L' and 'E' and we believe that the Applicant intends to use that space for the lot number and expiration date. However, it is important that this information is clearly identified in case the Cimzia syringe is removed from or is not stored in the original carton. The abbreviations 'L' and 'E' are not commonly understood. We prefer that such abbreviations be avoided so that healthcare practitioners and patients can readily identify these items.

The syringe label and carton labeling should prominently feature a statement conveying the net quantity of product (in terms of total milliliters contained in each syringe) on the principal display panel. It is important for healthcare providers to be able to accurately determine the contents of each syringe, especially when dispensing the product and when calculating or preparing the dose to be administered.

The prefilled syringes are fixed dose and intended for a single use. Thus for safety reasons, the syringes (if space permits) should include a statement that each syringe is intended for a single use and any remaining product in the syringe should be discarded after a single use. It is important for the healthcare practitioner or patient administering the dose to understand that the syringe contains a single dose and it is single use, so that any remaining product (e.g., overfill) for another dose or another patient will not be retained.

4.3 Carton Labeling

The carton labeling should prominently feature a statement conveying the net quantity of product (in terms of total milliliters contained in each syringe) on the principal display panel. It is important for healthcare providers or patients to be able to accurately determine the contents of each syringe especially when dispensing the product and when calculating or preparing the dose to be administered.

The prefilled syringes are fixed dose and intended for a single use. Thus for safety reasons, the carton labeling should include a statement that each syringe is intended for a single use and any remaining product in the syringe should be discarded after a single use. It is important for the healthcare practitioner administering the dose to understand that the syringe contains a single dose and it is single use, so that any remaining product (e.g., overfill) for another dose or another patient will not be retained.

DMEPA believes the statement "no US standard of potency" does not serve any purpose for safety or efficacy for this product. Furthermore, it is confusing and may create questions about dosing. Since there is a recommended dose of Cimzia (either 200 mg or 400 mg) with a standard unit of strength (milligram), this statement is unnecessary, confusing, and probably meaningless to the majority of healthcare practitioners.

The promotional statement "Syringe designed in partnership with OXO Good Grip" (with logo) is distracting and takes up needed space on the carton. Such a statement is not important to the safe or effective use of this product, and distracts away from the important information necessary for use of the product when featured so prominently on the principal display panel.

4.4 Prescribing Information Labeling

When evaluating the insert labeling, we noted information that is presented in an inconsistent or otherwise confusing manner which may lead to confusion or inappropriate or incorrect dosing.

DMEPA notes that the Dosage and Administration section of the Highlights of Prescribing Information is not consistent with the Dosage and Administration section under the Full Prescribing Information. Specifically, the text in the Highlights of Prescribing Information does not convey that the 400 mg dose is comprised of two subcutaneous injections of 200 mg. It is important to emphasize this fact to the user to avoid confusion or incorrect dosing. We foresee cases in which the user assumes the entire dose is contained in a single syringe, resulting in the administration of a single syringe, resulting in a potential underdose with 200 mg of Cimzia.

The insert labeling (e.g., section 17.2) should contain a warning to patients and healthcare providers that they should not attempt to place the needle cover back on the used syringe or otherwise recap the needle. DMEPA continues to see reports of patient harm that occur when both patients and healthcare practitioners attempt to recap a used needle and specific warnings against this practice should be included in the insert labeling and the Medication Guide.

4.5 Medication Guide

The Medication Guide should clearly state that two syringes of 200 mg must be administered to comprise a dose of 400 mg. It is important that patients and healthcare practitioners, especially those dispensing Cimzia or those preparing to administer Cimzia, are able to recognize that a dose of 400 mg requires administration by two separate injections of 200 mg each. If the person administering the dose does not recognize this fact, the patient will receive only one half of the recommended dose.

The Medication Guide should contain a warning to patients and healthcare providers that they should not attempt to place the needle cover back on the syringe or otherwise recap the needle, as discussed in section 4.4 above.

4.6 Prefilled Syringes

(b) (4) It is important for the label to be legible so that it can be read by the healthcare professional or patient who is preparing and administering the dose. Currently, the entire syringe of Cimzia (200 mg) will be administered for a dose (b) (4), however in the future there may be a need to give partial doses from the 200 mg syringe, (b) (4)

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduce vulnerability to confusion that could lead to medication errors. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug

approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

Based upon our assessment of the labels and labeling, and the review of post-marketing medication error reports, the Division of Medication Error Prevention and Analysis has identified areas needed of improvement. We have provided recommendations in section 5.2 and request this information be forwarded to the Applicant. We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Cheryl Wiseman, Project Manager, at 301-796-0567.

5.2 COMMENTS TO THE APPLICANT

5.2.1 General Comments

1. DMEPA finds the proposed changes to the Cimplicity Distribution and Specialty Pharmacy Network acceptable from a medication error perspective, since these measures will limit access to the lyophilized powder, and the prefilled syringes will be the default dosage form to be dispensed.

5.2.2 Syringe Labels

1. Increase the prominence and readability of the strength (e.g., 200 mg/mL) using a larger font and brighter or darker colors, as necessary, and ensure that it prominent and legible.
2. Add the text "Lot" and "Expiration Date" to the syringe label rather than using the abbreviations "L" and "E" so that this information is clearly communicated. If the words "Expiration Date" cannot be accommodated due to space limitations, we recommend consideration be given to using the expressions "Expiration", "Exp. Date", or "Exp" to identify the expiration date of the product.
3. Add a statement to the syringe label indicating that "each syringe contains 1 mL of Cimzia".
4. Add a statement that each syringe is for "single use" (or something similar).

5.2.3 Carton Labeling

1. Add a statement to the principal display panel that "each syringe is intended for a single use and any remaining product in the syringe should be discarded after a single use" (or something similar).
2. Remove the statement "no US standard of potency" from the carton labeling as it is confusing and meaningless to healthcare practitioners.
3. Relocate the "Syringe designed in partnership with OXO Good Grip" statement so that it is no longer featured on the principal display panel. As currently located, this statement is distracting, and it is not necessary for the safe and effective use of the product.

5.2.4 Prescribing Information Labeling

1. In the Highlights of Prescribing Information (Dosage and Administration section), state that the initial dose of Cimzia is "400 mg (given as two subcutaneous injections of 200 mg)", by including the text in parentheses.

2. Include a warning to patients and healthcare providers that they should not attempt to place the needle cover back on the syringe or otherwise recap the needle. DMEPA recommends this information be conveyed within section 17.2.

5.2.5 Medication Guide

1. The Medication Guide should clearly state that two syringes of 200 mg must be administered to comprise a dose of 400 mg. If the person administering the dose does not easily recognize this, the patient will receive only one half of the recommended dose. DMEPA recommends that this information be conveyed several times in the Medication Guide, for example in the "What do I need to do to prepare and give an injection of Cimzia" and the "Preparing to use the pre-filled syringe" sections.
2. Include a warning to patients and healthcare providers that they should not attempt to place the needle cover back on the syringe or otherwise recap the needle. DMEPA recommends this information be conveyed within the bulleted step-by-step instructions as well as the "How should I dispose of needles and syringes" sections.

5.2.6 Prefilled Syringes

1. We recommend that the placement of the syringe label be offset to the side so the calibrations and the syringe label can be clearly read. It is important for the healthcare professional and the patient to be able to read the label especially when preparing and administering the dose.

2 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/S-080

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125271/0

OCT - 3 2008

UCB, Inc.
1950 Lake Park Drive
Smyrna, GA 30080

Attention: Sandra Bonsall, RAC
Associate Director, Regulatory Affairs

Dear Ms. Bonsall:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for CIMZIA® (certolizumab pegol).

We received your September 30, 2008 amendment to this application on October 1, 2008 and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to January 4, 2009, to provide time for a full review of the amendment.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Kathleen Davies, at (301) 796-2205.

Sincerely,

Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Hughes, Patricia

From: Hoyt, Colleen
Sent: Wednesday, October 01, 2008 6:06 PM
To: Hughes, Patricia
Cc: Rivera Martinez, Edwin; Rosa, Carmelo R; Cruz, Concepcion; Ferguson, Shirnette D; Kiel, Hea S
Subject: FW: Comments on limited Review of FD-483s issued to (b) (4)

Follow Up Flag: Follow up
Flag Status: Yellow

Patricia:

Based on a review of the two (b) (4) 483's, a recommendation to withhold approval of STN 125271 has been made until further information is available for review. I suggest if you have questions regarding this decision, you should contact Carmelo Rosa or Edwin.

Colleen

From: Rosa, Carmelo R
Sent: Wednesday, October 01, 2008 4:34 PM
To: Hoyt, Colleen; Adams, Shawnte L; Charity, Anthony
Cc: Rivera Martinez, Edwin
Subject: Comments on limited Review of FD-483s issued to (b) (4)

Hi Shawnte/Hoyt Collen

Anthony Charity requested that I performed a review of two 483s issued by Tom Arista, DFI National Expert, to different sites of (b) (4) located in (b) (4)

Based on the limited information available (no EIR, no Exhibits, no written response for review and no details or explanations of the specific issues raised), along with no specific information related to the potential risk, a conclusion to approve the applications involving the two below referenced facilities is not recommended.

I. (b) (4)

II. (b) (4)

III. NO OTHER FD-483 WAS RECEIVED FOR REVIEW

NOTE:
Additional information related to the (b) (4) . We also consider significant both firms inability to determine or conduct a root cause analysis. Therefore, a written response is also imperative to evaluate the above firms written commitments to address the issues raised.

Carmelo Rosa,
DMPQ Compliance Officer

Hughes, Patricia

From: Hoyt, Colleen
Sent: Wednesday, October 01, 2008 2:20 PM
To: Hughes, Patricia
Cc: Rivera Martinez, Edwin; Cruz, Concepcion; Ferguson, Shirnette D; Kiel, Hea S; Charity, Anthony
Subject: BLA 125271

The Manufacturing Assessment and Preapproval Compliance Branch has completed the review and evaluation of the TB-EER below. The inspection status of each firm listed in the application is below:

1. (b) (4)

A district inspection was conducted on (b) (4) and included profile BTP coverage. The inspection was classified VAI and is considered acceptable.

2. UCB Manufacturing, Inc., Rochester, NY 14623 FEI 1314625; (b) (4)

A district inspection was conducted on 11/30/07 for all profiles. The inspection was classified NAI and is considered acceptable.

3. (b) (4)

Recent inspection findings currently under review by ICT.

4. (b) (4)

Recent inspection findings currently under review by ICT.

5. (b) (4)

Recent inspection findings currently under review by ICT.

6. (b) (4)

No inspection information available in FACTS for assessment.

7. (b) (4)

No inspection information available in FACTS for assessment.

Colleen F. Hoyt
Consumer Safety Officer/DMPQ Biotech Liaison
U.S. Food and Drug Administration
CDER/OC/DMPQ
o - (301) 796-3251

f - (301) 842-8742
colleen.hoyt@fda.hhs.gov

10903 New Hampshire Avenue
WO51-Room 4308
Silver Spring, MD 20993

From: Cruz, Concepcion
Sent: Wednesday, October 01, 2008 1:42 PM
To: Kiel, Hea S; Ferguson, Shirnette D; Hoyt, Colleen
Cc: Rivera Martinez, Edwin
Subject: FW: BLA 125271
Importance: High

All,

who is working in these TB-EERs? Please f/u with ICT. They're currently reviewing the (b) (4) sites.

Coki Cruz
301-796-3254 voice
301-847-8742 fax

From: Rivera Martinez, Edwin
Sent: Wednesday, October 01, 2008 1:26 PM
To: Cruz, Concepcion
Subject: FW: BLA 125271

Coki:

Please follow-up on these TB EERs. We need responses ASAP due to upcoming PDUFA date.

Edwin

From: Hughes, Patricia
Sent: Tuesday, September 30, 2008 1:19 PM
To: Hoyt, Colleen; Ferguson, Shirnette D; Kiel, Hea S
Cc: Rivera Martinez, Edwin
Subject: FW: BLA 125271

The PDUFA date is this week. What is the verdict on these sites. Can I have something in writing before the due date. We have essentially missed all the GRMP action dates.

Patricia

From: Hughes, Patricia
Sent: Monday, August 25, 2008 12:13 PM
To: CDER-TB-EER
Cc: Hughes, Patricia
Subject: BLA 125271

Please conduct the following evaluations in support of BLA 125271 from UCB for Cimzia, PDUFA

date October 5, 2008.

1. [redacted]
2. UCB Manufacturing, Inc., Rochester, NY 14623 FEI 1314625; [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]

Thank you.

Patricia

Mills, Sharon

From: Mills, Sharon
Sent: Monday, September 22, 2008 9:20 AM
To: Siegel, Jeffrey
Cc: Davies, Kathleen; Duckhorn, Jodi; Wheeler, Chris
Subject: RE: BLA 125271 Cimzia--DRISK revisions to MG based on our discussion

Jeff,

Very good, thanks for the clarification. We appreciate it. Given the small differences, I wanted to ask for the sake of consistency. Kathleen can remove the yellow highlight on " (b) (4) in the MG and then I think we are good to go.

Sharon

From: Siegel, Jeffrey
Sent: Monday, September 22, 2008 9:10 AM
To: Mills, Sharon
Cc: Davies, Kathleen; Duckhorn, Jodi; Wheeler, Chris
Subject: RE: BLA 125271 Cimzia--DRISK revisions to MG based on our discussion

Sharon,

Regarding the issue of including (b) (4) I would favor not including that. (b) (4) Given that the differences were small in the AE table I don't think it makes sense to include (b) (4) as an AE in the MG. Regarding (b) (4) we did not identify (b) (4) as an AE that was consistently observed. Again since the differences were small in the AE table if our goal is to provide useful information to patients I don't think it's necessary to include (b) (4) Finally for (b) (4) I checked it off on purpose. (b) (4)

Jeff

From: Mills, Sharon
Sent: Monday, September 22, 2008 9:01 AM
To: Siegel, Jeffrey
Cc: Davies, Kathleen; Duckhorn, Jodi; Wheeler, Chris
Subject: RE: BLA 125271 Cimzia--DRISK revisions to MG based on our discussion

Thanks Jeff. Please just clarify about (b) (4) and (b) (4) (see my original email). There are only 1% differences with these also.

Sharon

From: Siegel, Jeffrey
Sent: Monday, September 22, 2008 8:32 AM
To: Mills, Sharon
Cc: Davies, Kathleen; Duckhorn, Jodi; Wheeler, Chris
Subject: RE: BLA 125271 Cimzia--DRISK revisions to MG based on our discussion

Sharon,

Thanks for getting thes revisions back to us so quickly. They look just fine to me.

Jeff

From: Mills, Sharon
Sent: Monday, September 22, 2008 8:14 AM
To: Siegel, Jeffrey

Cc: Davies, Kathleen; Duckhorn, Jodi; Wheeler, Chris
Subject: RE: BLA 125271 Cimzia--DRISK revisions to MG based on our discussion

Hi Jeff,

I noticed after sending that I did not include the words "for RA" in the sentence about the biologics and TNF blockers under "Tell your doctor about all the medicines you take..." Please use this corrected version. The questions/comments below in my email from last night still apply. That is what I get for doing this at night.

Thanks,
Sharon

<< File: DRISK revisions_Cimzia MG DRISK clean copy 9-11-2008.doc >>

From: Mills, Sharon
Sent: Sunday, September 21, 2008 10:09 PM
To: Siegel, Jeffrey
Cc: Davies, Kathleen; Duckhorn, Jodi; Wheeler, Chris
Subject: BLA 125271 Cimzia--DRISK revisions to MG based on our discussion

Hi Jeff,

This is in follow-up to our meeting on Friday to go over some of your questions and suggested revisions to the MG based on our recent review. I made the discussed changes as tracked changes to the clean copy of the MG that we provided you with so that you can better identify the new changes. I deleted our previous comments where we addressed the changes.

When I went to insert my changes into the MG document, (b) (4)

(b) (4)

Please look at the MG and the PI and let me know your concurrence so that we can try to wrap things up for you as requested.

Thanks,
Sharon

<< File: DRISK revisions_Cimzia MG DRISK clean copy 9-11-2008.doc >>

Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Division of Risk Management
FDA/CDER/OSE
10903 New Hampshire Avenue
Bldg. 22, room 4485
Mailstop 4447
Silver Spring, MD 20993-0002
Phone: 301.796.2036
Fax: 301.796.9837
email: sharon.mills@fda.hhs.gov

Hughes, Patricia

From: Mozzachio, Alicia (CDER)
Sent: Thursday, July 10, 2008 11:37 AM
To: Hughes, Patricia
Cc: Rivera Martinez, Edwin
Subject: FW: (b)(4) Inspections

Follow Up Flag: Follow up
Flag Status: Blue

Attachments: RE: Audit Request at (b)(4) RE: Audit Request at (b)(4) RE: Audit Request at (b)(4) Audit Request at (b)(4)

Patricia,

I spoke with DFI today. Please read below. the firm did not agree to the initial inspection request for (b)(4) and proposed (b)(4) DFI said no that we had to come in September. Thomas Arista is the investigator. The team is leaving (b)(4). The fact that (b)(4) declined the initial request should be enough to "withhold" or stop the clock so we don't miss our deadline.

The inspection planning is underway. DMPQ should not be planning to do these inspections. DFI did what they had to do.

Thanks.
Alicia

From: Blosser, Barbara J
Sent: Thursday, July 10, 2008 11:32 AM
To: Mozzachio, Alicia (CDER)
Subject: (b)(4) Inspections

Good morning Alicia,

I am forwarding on to you the communications with (b)(4) in (b)(4) regarding scheduling inspections.

Please note that initially I attempted to scheduled the three inspections to start in the middle of (b)(4) (b)(4) was unable to accommodate this request. We negotiated an agreement to conduct the inspections beginning the (b)(4).

If you have any additional questions, please advise.

(b)(4)

Barbara J. Blosser
Management Analyst/International Program Specialist
FDA/ORO/DFI/International Operations
11630 West 80th Street
Lenexa, KS 66214
Tel: (913) 752-2466
Fax: (913) 752-2496
Barbara.Blosser@fda.hhs.gov