CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125160Orig1s283

Trade Name:	CIMZIA
Generic or Proper Name:	certolizumab pegol
Sponsor:	UCB, Inc.
Approval Date:	May 24, 2018
Indication:	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) • Treatment of adult patients with active psoriatic arthritis (1.3) • Treatment of adults with active ankylosing spondylitis (1.4) • Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (1.5)

CENTER FOR DRUG EVALUATION AND RESEARCH

125160Orig1s283

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Orig1s283

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125160/S-283

SUPPLEMENT APPROVAL

UCB, Inc.
Attention: Jennifer King
Regulatory Affairs Americas
1950 Lake Park Drive, Building 2100
Smyrna, GA 30080

Dear Ms. King:

Please refer to your Supplemental Biologics License Application (sBLA), dated July 24, 2017, received July 24, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for CIMZIA® (certolizumab pegol).

We also refer to our approval letter dated May 24, 2018 which contained the following errors:

- The submit and received date for the sBLA was noted as July 24, 2018. The sBLA submit and received date was July 24, 2017.
- On pages 2, 4, and 5 the referenced INDs (b) (4), respectively, are incorrect. The correct application is IND 100348.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain May 24, 2018, the date of the original approval letter.

This Prior Approval supplemental biologics application proposes a new indication for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is

identical to the enclosed labeling (text for the prescribing information, text for the patient package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.
Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 less than 6 years because necessary studies are impossible or highly impracticable. This is because:

- The prevalence of psoriasis in the 0 to less than 6 years age group is low (with the highest prevalence published of 0.3%) and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.

- Live vaccinations (MMR, varicella) are usually given in this age group, limiting the treatment of this pediatric population with certolizumab.

We are deferring submission of your pediatric study for ages 6 to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

3408-1	Conduct a Pharmacokinetics (PK), Safety, and Efficacy Study in pediatric subjects 6 to less than 18 years of age with moderate to severe psoriasis (with a duration of exposure to certolizumab pegol of at least one year).

The timetable you submitted on May 08, 2018 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2019
Study Completion:	02/2025
Final Report Submission:	12/2025

Submit the protocol to your IND 100348, with a cross-reference letter to this BLA.

Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes 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.

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 identify the unexpected serious risk: for the presence of binding and neutralizing anti-drug antibodies in the proposed population as well as an unexpected serious risk of maternal, fetal and infant toxicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3408-2	Utilize the validated immunogenicity assays developed under PMC 3408-5 and PMC 3408-6 to analyze the immunogenicity profile of certolizumab pegol using banked patient samples from Phase 3 trials CIMPASI-1, CIMPASI-2, and CIMPACT. Evaluate the impact of immunogenicity on pharmacokinetics, efficacy, and safety in subjects with psoriasis based on the immunogenicity data generated with the newly validated assays.

The timetable you submitted on May 08, 2018 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12//2018
Study Completion:	06/2019
Final Report Submission:	09/2019

3408-3 A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to certolizumab pegol during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, will be assessed through at least the first year of life. You may expand a current prospective registry to include women who are exposed to certolizumab pegol for the treatment of plaque psoriasis.

The timetable you submitted on May 08, 2018 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12//2019
Study Completion:	07/2029
Final Report Submission:	01/2030

3408-4 Conduct a retrospective cohort study using claims or electronic medical record data or a case control study to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths, and infant infections in women exposed to certolizumab pegol during pregnancy compared to an unexposed control population.

The timetable you submitted on May 08, 2018 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2020
Study Completion:	09/2026
Final Report Submission:	09/2027

Submit the protocol(s) to your IND 100348, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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 601.70 to 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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3408-5 Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to certolizumab pegol, including procedures for the accurate detection of binding antibodies to certolizumab pegol in the presence of certolizumab pegol levels expected in the serum or plasma at the time of patient sampling. In addition, an assessment of the contribution of binding antibodies to PEG should also be evaluated.

The timetable you submitted on May 08, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2018

3408-6 Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to certolizumab pegol, including procedures for the accurate detection of neutralizing antibodies to certolizumab pegol in the presence of certolizumab pegol levels that are expected in the serum or plasma at the time of patient sampling.

The timetable you submitted on May 08, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2018

Submit clinical protocols to your IND 100348 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should

include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Barbara Gould, Chief, Project Management Staff, at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDALL A MARCUS
05/24/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Orig1s283

LABELING

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) for injection, for subcutaneous use
CIMZIA (certolizumab pegol) injection, for subcutaneous use
Initial U.S. Approval: 2008

WARNING: SERIOUS INFECTIONS AND MALIGNANCY
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 (5.1).**
- **CIMZIA should be discontinued if a patient develops a serious infection or sepsis (5.1).**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting CIMZIA (5.1).**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative (5.1)**
- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CIMZIA is a member (5.2). CIMZIA is not indicated for use in pediatric patients. (8.4)**

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

Indications and Usage (1.5)	05/2018
Dosage and Administration (2.5)	05/2018
Contraindications (4)	05/2018

----------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)
- Treatment of adult patients with active psoriatic arthritis. (1.3)
- Treatment of adults with active ankylosing spondylitis (1.4)
- Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (1.5)

----------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)(2).

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

Psoriatic Arthritis (2.3)

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

Ankylosing Spondylitis (2.4)

- 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks.

Plaque Psoriasis (2.5, 14.5)

- 400 mg (given as 2 subcutaneous injections of 200 mg each) every other week. For some patients (with body weight ≤ 90 kg), a dose of 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and at Weeks 2 and 4, followed by 200 mg every other week may be considered.

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

- For injection: 200 mg lyophilized powder in a single-dose vial (3)
- Injection: 200 mg/mL solution in a single-dose prefilled syringe (3)

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

- Serious hypersensitivity reaction to certolizumab pegol or to any of the excipients. (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)
- Invasive fungal infections – for patients who develop a systemic illness on CIMZIA, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic (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 – test for HBV infection before starting CIMZIA. 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 – avoid use 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: 05/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

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, including Legionella and Listeria.**

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)].*

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CIMZIA is a member *[see Warnings and Precautions (5.2)].* CIMZIA is not indicated for use in pediatric patients.

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).

1.3 Psoriatic Arthritis

CIMZIA is indicated for the treatment of adult patients with active psoriatic arthritis (PsA).

1.4 Ankylosing Spondylitis

CIMZIA is indicated for the treatment of adults with active ankylosing spondylitis (AS). *[see Clinical Studies (14.4)]*

1.5 Plaque Psoriasis

CIMZIA is indicated for the treatment of adults with moderate-to-severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy *[see Clinical Studies (14.5)]*

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 Psoriatic Arthritis

The recommended dose of CIMZIA for adult patients with psoriatic arthritis is 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and at week 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 (14.3)]*.

2.4 Ankylosing Spondylitis

The recommended dose of CIMZIA for adult patients with ankylosing spondylitis is 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and at weeks 2 and 4, followed by 200 mg every 2 weeks or 400 mg every 4 weeks.

2.5 Plaque Psoriasis

The recommended dose of CIMZIA for adults with moderate-to-severe plaque psoriasis is 400 mg (given as 2 subcutaneous injections of 200 mg each) every other week.

For some patients (with body weight ≤ 90 kg), CIMZIA 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and at Weeks 2 and 4, followed by 200 mg every other week can be considered *[see Clinical Studies (14.5)]*.

2.6 Preparation and Administration of CIMZIA Using the Lyophilized Powder for Injection

CIMZIA 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 *[see*

How Supplied/Storage and Handling (16)]. Step-by-step preparation and administration instructions are provided below.

Preparation and Storage

a. Remove CIMZIA from the refrigerator and allow the vial(s) to sit at room temperature for 30 minutes before reconstituting. Do not warm the vial in any other way. Use appropriate aseptic technique when preparing and administering CIMZIA.
b. Reconstitute the vial(s) of CIMZIA with 1 mL of Sterile Water for Injection, USP using the 20-gauge needle provided. The sterile water for injection should be directed at the vial wall rather than directly on CIMZIA.
c. Gently swirl each vial of CIMZIA for about one minute without shaking, assuring that all of the powder comes in contact with the Sterile Water for Injection. The swirling should be as gentle as possible in order to avoid creating a foaming effect.
d. Continue swirling every 5 minutes as long as non-dissolved particles are observed. Full reconstitution may take as long as 30 minutes. The final reconstituted solution contains 200 mg/mL and should be clear to opalescent, colorless to pale yellow liquid essentially free from particulates.
e. Once reconstituted, CIMZIA can be stored in the vials for up to 24 hours between 2° to 8° C (36° to 46° F) prior to injection. Do not freeze.

Administration

a. Prior to injecting, reconstituted CIMZIA should be at room temperature but do not leave reconstituted CIMZIA at room temperature for more than two hours prior to administration.
b. Withdraw the reconstituted solution into a separate syringe for each vial using a new 20-gauge needle for each vial so that each syringe contains 1 mL of CIMZIA (200 mg of certolizumab pegol).
c. Replace the 20-gauge needle(s) on the syringes with a 23-gauge(s) for administration.
d. Inject the full contents of the syringe(s) subcutaneously, by pinching the skin of the thigh or abdomen. Where a 400 mg dose is required, two injections are required, therefore, separate sites should be used for each 200 mg injection.

2.7 Preparation and Administration of CIMZIA Using the Prefilled Syringe

After proper training in subcutaneous injection technique, a patient may self-inject with the CIMZIA Prefilled Syringe if a physician determines that it is appropriate.

Patients using the CIMZIA Prefilled Syringe should be instructed to inject the full amount in the syringe (1 mL), according to the directions provided in the Instructions for Use booklet.

2.8 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.

2.9 Concomitant Medications

CIMZIA may be used as monotherapy or concomitantly with non-biological disease modifying anti-rheumatic drugs (DMARDs).

The use of CIMZIA in combination with biological DMARDs or other tumor necrosis factor (TNF) blocker therapy is not recommended.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 200 mg of lyophilized powder in a single-dose vial for reconstitution

Injection: 200 mg/mL clear to opalescent, colorless to pale yellow solution in a single-dose prefilled syringe

4 CONTRAINDICATIONS

CIMZIA is contraindicated in patients with a history of hypersensitivity reaction to certolizumab pegol or to any of the excipients. Reactions have included angioedema, anaphylactoid reaction, serum sickness, and urticaria *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Infections

[see Boxed Warning]

Patients treated with CIMZIA are at an increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with CIMZIA should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants (e.g. corticosteroids or methotrexate) may be at a greater risk of infection. 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
- with a history of an opportunistic infection
- 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

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving CIMZIA, including patients who have previously or concomitantly received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test 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. Prior to initiating CIMZIA, assess if treatment for latent tuberculosis is needed; and consider an induration of 5 mm or greater a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy 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. Despite previous or concomitant treatment for latent tuberculosis, cases of active tuberculosis have occurred in patients treated with CIMZIA. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with CIMZIA. 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.

Strongly consider tuberculosis 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.

Monitoring

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.

Invasive Fungal Infections

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. During CIMZIA studies of psoriasis, malignancies (excluding non-melanoma skin cancer) were observed corresponding to an incidence rate of 0.5 (0.2, 1.0) per 100 subject-years among a total of 995 subjects who received CIMZIA. The size of the control group and limited duration of the controlled portions of the studies precludes the ability to draw firm conclusions.

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy $\leq$ 18 years of age), of which CIMZIA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1

to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous post-marketing reports. CIMZIA is not indicated for use in pediatric patients.

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. In the CIMZIA PsO clinical trials (placebo-controlled and open label) there was one case of Hodgkin's 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 *[see Adverse Reactions (6.1)]*. The potential role of TNF blocker therapy in the development of malignancies in adults is not known.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma that has a very aggressive disease course and is usually fatal, have been reported in patients treated with TNF blockers, including CIMZIA. The majority of reported TNF blocker cases occurred in adolescent and young adult males with Crohn's disease or ulcerative colitis. Almost all of these patients had received treatment with the immunosuppressants azathioprine and/or 6-mercaptopurine (6-MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk of using a TNF blocker in combination with azathioprine or 6-MP should be carefully considered.

Cases of acute and chronic leukemia have been reported in association with post-marketing TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-antagonists, including CIMZIA. Periodic skin examinations are recommended for all patients, particularly those with risk factors for skin cancer.

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, anaphylactoid reaction, dyspnea, hypotension, rash, serum sickness, and urticaria. Some of these reactions occurred after the first administration of CIMZIA. 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, has been associated with 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.

Test patients for HBV infection before initiating treatment with CIMZIA. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. 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, of which CIMZIA is a member, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, and with peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of CIMZIA in patients with pre-existing or recent-onset central or peripheral 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 *[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 etanercept 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

Patients treated with CIMZIA may receive vaccinations, except for live or live attenuated vaccines. No data are available on the response to live vaccinations or the secondary transmission of infection by live vaccines in patients receiving CIMZIA.

In a placebo-controlled clinical trial of patients with rheumatoid arthritis, no difference was detected in antibody response to vaccine between CIMZIA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with CIMZIA. Similar proportions of patients developed protective levels of anti-vaccine antibodies between CIMZIA and placebo treatment groups; however patients receiving CIMZIA and concomitant methotrexate had a lower humoral response compared with patients receiving CIMZIA alone. The clinical significance of this is unknown.

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

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)]*

6.1 Clinical Trials Experience

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.

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%).

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.

Psoriatic Arthritis Clinical Study

CIMZIA has been studied in 409 patients with psoriatic arthritis (PsA) in a placebo-controlled trial. The safety profile for patients with PsA treated with CIMZIA was similar to the safety profile seen in patients with RA and previous experience with CIMZIA.

Ankylosing Spondylitis Clinical Study

CIMZIA has been studied in 325 patients with axial spondyloarthritis of whom the majority had ankylosing spondylitis (AS) in a placebo-controlled study (AS-1). The safety profile for patients in study AS-1 treated with CIMZIA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

In clinical studies, a total of 1112 subjects with plaque psoriasis were treated with CIMZIA. Of these, 779 subjects were exposed for at least 12 months, 551 for 18 months, and 66 for 24 months.

Data from three placebo-controlled studies (Studies PS-1, PS-2, and PS-3) in 1020 subjects (mean age 46 years, 66% males, 94% white) were pooled to evaluate the safety of CIMZIA [see Clinical Studies (14)].

Placebo-Controlled Period (Week 0-16)
In the placebo-controlled period of Studies PS-1, PS-2 and PS-3 in the 400 mg group, adverse events occurred in 63.5% of subjects in the CIMZIA group compared to 61.8% of subjects in the placebo group. The rates of serious adverse events were 4.7% in the CIMZIA group and 4.5% in the placebo group. Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the CIMZIA group than in the placebo group.

Table 2: Adverse Reactions Occurring in ≥1% of Subjects in the CIMZIA Group and More Frequently than in the Placebo Group in the Plaque Psoriasis Studies PS-1, PS-2, and PS-3.

Adverse Reactions	Cimzia 400 mg every other week n (%) N=342	Cimzia 200 mg [5] every other week n (%) N=350	Placebo n (%) N=157
Upper respiratory tract infections[1]	75 (21.9)	68 (19.4)	33 (21.0)
Headache[2]	13 (3.8)	10 (2.9)	4 (2.5)
Injection site reactions[3]	11 (3.2)	6 (1.7)	1 (0.6)
Cough	11 (3.2)	4 (1.1)	3 (1.9)
Herpes infections[4]	5 (1.5)	5 (1.4)	2 (1.3)

1: Upper respiratory tract infection cluster includes upper respiratory tract infection, pharyngitis bacterial, pharyngitis streptococcal, upper respiratory tract infection bacterial, viral upper respiratory tract infection, viral pharyngitis, viral sinusitis, and nasopharyngitis.
2: Headache includes headache and tension headache.
3: Injection site reactions cluster includes injection site reaction, injection site erythema, injection site bruising, injection site discoloration, injection site pain, and injection site swelling.
4: Herpes infections cluster includes oral herpes, herpes dermatitis, herpes zoster, and herpes simplex.
5: Subjects received 400 mg of CIMZIA at Weeks 0, 2, and 4, followed by 200 mg every other week.

Elevated Liver Enzymes
Elevated liver enzymes were reported more frequently in the CIMZIA-treated subjects (4.3% in the 200 mg group and 2.3% in the 400 mg group) than in the placebo-treated subjects (2.5%). Of CIMZIA-treated subjects who had elevation of liver enzymes, two subjects were discontinued from the trial. In controlled Phase 3 studies of CIMZIA in adults with PsO with a controlled period duration ranging from 0 to 16 weeks, AST and/or ALT elevations ≥5 x ULN occurred in 0.9% of CIMZIA 200 mg or CIMZIA 400 mg arms and none in placebo arm.

Psoriasis-Related Adverse Events
In controlled clinical studies in psoriasis, change of plaque psoriasis into a different psoriasis sub-types (including erythrodermic, pustular and guttate), was observed in <1% of Cimzia treated subjects.

Adverse Reactions of Special Interest Across Indications
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)]*.

In controlled clinical studies in psoriasis, the incidence rates of infections were similar in the CIMZIA and placebo groups. The infections consisted primarily of upper respiratory tract infections and viral infections (including herpes infections). Serious adverse events of infection occurred in CIMZIA-treated patients during the placebo-controlled periods of the pivotal studies (pneumonia, abdominal abscess, and hematoma infection) and Phase 2 study (urinary tract infection, gastroenteritis, and disseminated tuberculosis).

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. Reports include cases of disseminated (miliary, lymphatic, and 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. In Phase 2 and Phase 3 studies with CIMZIA in plaque psoriasis, there were 2 cases of TB among 1112 exposed patients *[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 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)]*.

6.2 Immunogenicity

Patients with Crohn's disease were tested at multiple time points for antibodies to certolizumab pegol during Studies CD1 and CD2. In patients continuously exposed to CIMZIA, the overall percentage of patients who were antibody positive to CIMZIA on at least one occasion was 8%; 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.

In two long-term (up to 7 years of exposure), open-label Crohn's disease studies, overall 23% (207/903) of patients developed antibodies against certolizumab pegol on at least one occasion. Of the 207 patients who were antibody positive, 152 (73%) had a persistent reduction of drug plasma concentration, which represents 17% (152/903) of the study population. The data from these two studies do not suggest an association between the development of antibodies and adverse events.

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.

Approximately 8 % (22/265) and 19% (54/281) of subjects with psoriasis who received CIMZIA 400 mg every 2 weeks and CIMZIA 200 mg every 2 weeks for 48 weeks, respectively, developed antibodies to certolizumab pegol. Of the subjects who developed antibodies to certolizumab pegol, 45% (27/60) had antibodies that were classified as neutralizing. Antibody formation was associated with lowered drug plasma concentration and reduced efficacy.

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 methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. The assay used to measure antibodies to certolizumab pegol is subject to interference by serum certolizumab pegol, possibly resulting in an underestimation of the incidence of antibody formation. For these reasons, comparison of the incidence of antibody positivity 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)]*.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of CIMZIA. 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.

Vascular disorder: systemic vasculitis has been identified during post-approval use of TNF blockers.

Skin: case of severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and new or worsening psoriasis (all sub-types including pustular and palmoplantar) have been identified during post-approval use of TNF blockers.

Immune System Disorders: sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Melanoma, Merkel cell carcinoma (neuroendocrine carcinoma of the skin) *[see Warnings and Precautions (5.2)]*.

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

Avoid use of 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 Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to CIMZIA during pregnancy. For more information, healthcare providers or patients can contact:

MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS). The OTIS AutoImmune Diseases Study at 1-877-311-8972 or visit http://mothertobaby.org/pregnancy-studies/

Risk Summary

Limited data from the ongoing pregnancy registry on use of CIMZIA in pregnant women are not sufficient to inform a risk of major birth defects or other adverse pregnancy outcomes. However, certolizumab pegol plasma concentrations obtained from two studies of CIMZIA use during the third trimester of pregnancy demonstrated that placental transfer of certolizumab pegol was negligible in most infants at birth, and low in other infants at birth *(see Data)*. There are risks to the mother and fetus associated with active rheumatoid arthritis or Crohn's disease. The theoretical risks of administration of live or live-attenuated vaccines to the infants exposed *in utero* to CIMZIA should be weighed against the benefits of vaccinations *(see Clinical Considerations)*. No adverse developmental effects were observed in animal reproduction studies during which pregnant rats were administered intravenously a rodent anti-murine TNFα pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol during organogenesis at up to 2.4 times the recommended human dose of 400 mg every four weeks.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with rheumatoid arthritis or Crohn's disease is correlated with maternal disease activity and that active disease increases the risk of adverse pregnancy outcomes, including fetal loss, preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) and small for gestational age birth.

Fetal/Neonatal Adverse Reactions

Due to its inhibition of TNFα, CIMZIA administered during pregnancy could affect immune responses in the *in utero*-exposed newborn and infant. The clinical significance of BLQ or low levels is unknown for *in utero*-exposed infants. Additional data available from one exposed infant suggest that CIMZIA may be eliminated at a slower rate in infants than in adults *(see Data)*. The safety of administering live or live-attenuated vaccines in exposed infants is unknown.

Data

Human Data

A limited number of pregnancies have been reported in the ongoing pregnancy exposure registry. Due to the small number of CIMZIA-exposed pregnancies with known outcomes (n=54), no meaningful comparisons between the exposed group and control groups may be conducted to determine an association with CIMZIA and major birth defects or adverse pregnancy outcomes.

A multicenter clinical study was conducted in 16 women treated with CIMZIA at a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks during the third trimester of pregnancy for rheumatological diseases or Crohn's disease. The last dose of CIMZIA was given on average 11 days prior to delivery (range 1 to 27 days). Certolizumab pegol plasma concentrations were measured in samples from mothers and infants using an assay that can measure certolizumab pegol concentrations at or above 0.032 mcg/mL. Certolizumab pegol plasma concentrations measured in the mothers at delivery (range: 4.96 to 49.4 mcg/mL) were consistent with non-pregnant women's plasma concentrations in Study RA-I *[see Clinical Studies (14.2)]*. Certolizumab pegol plasma concentrations were not measurable in 13 out of 15 infants at birth. The concentration of certolizumab pegol in one infant was 0.0422 mcg/mL at birth (infant/mother plasma ratio of 0.09%). In a second infant, delivered by emergency Caesarean section, the concentration was 0.485 mcg/mL (infant/mother plasma ratio of 4.49%). At Week 4 and Week 8, all 15 infants had no measurable concentrations. Among 16 exposed infants, one serious adverse reaction was reported in a neonate who was treated empirically with intravenous antibiotics due to an increased white blood cell count; blood cultures were negative. The certolizumab pegol plasma concentrations for this infant were not measurable at birth, Week 4, or Week 8.

In another clinical study conducted in 10 pregnant women with Crohn´s disease treated with CIMZIA (400 mg every 4 weeks for every mother), certolizumab pegol concentrations were measured in maternal blood as well as in cord and infant blood at the day of birth with an assay that can measure concentrations at or above 0.41 mcg/mL. The last dose of CIMZIA was given on average 19 days prior to delivery (range 5 to 42 days). Plasma certolizumab pegol concentrations ranged from not measurable to 1.66 mcg/mL in cord blood and 1.58 mcg/mL in infant blood; and ranged from 1.87 to 59.57 mcg/mL in maternal blood. Plasma certolizumab pegol concentrations were lower (by at least 75%) in the infants than in mothers suggesting low placental transfer of certolizumab pegol. In one infant, the plasma certolizumab pegol concentration declined from 1.02 to 0.84 mcg/mL over 4 weeks suggesting that certolizumab pegol may be eliminated at a slower rate in infants than adults.

Animal Data

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. Animal reproduction studies have been performed in rats during organogenesis at intravenous doses up to 100 mg/kg (about 2.4 times the recommended human dose of 400 mg, based on the surface area) and have revealed no evidence of harm to the fetus due to cTN3 PF.

8.2 Lactation

Risk Summary

In a multicenter clinical study of 17 lactating women treated with CIMZIA at 200 mg every 2 weeks or 400 mg every 4 weeks, minimal certolizumab pegol concentrations were observed in breast milk. No serious adverse reactions were noted in the 17 infants in the study. There are no data on the effects on milk production. In a separate study, certolizumab pegol concentrations were not detected in the plasma of 9 breastfed infants at 4 weeks post-partum *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CIMZIA and any potential adverse effects on the breastfed infant from CIMZIA or from the underlying maternal condition.

Data

A multicenter clinical study designed to evaluate breast milk was conducted in 17 lactating women who were at least 6 weeks post-partum and had received at least 3 consecutive doses of CIMZIA 200 mg every 2 weeks or 400 mg every 4 weeks for rheumatological disease or Crohn's disease. The effects of certolizumab pegol on milk production were not studied. The concentration of certolizumab pegol in breast milk was not measurable in 77 (56 %) of the 137 samples taken over the dosing periods using an assay that can measure certolizumab pegol concentrations at or above 0.032 mcg/mL. The median of the estimated average daily infant doses was 0.0035 mg/kg/day (range: 0 to 0.01 mg/kg/day).

The percentage of the maternal dose (200 mg CIMZIA dosed once every 2 weeks), that reaches an infant ranged from 0.56% to 4.25% based on samples with measurable certolizumab pegol concentration. No serious adverse reactions were noted in the 17 breastfed infants in the study.

In a separate study, plasma certolizumab pegol concentrations were collected 4 weeks after birth in 9 breastfed infants whose mothers had been currently taking CIMZIA (regardless of being exclusively breastfed or not). Certolizumab pegol in infant plasma was not measurable i.e., below 0.032 mcg/mL.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Due to its inhibition of TNFα, CIMZIA administered during pregnancy could affect immune responses in the *in utero*-exposed newborn and infant *[see Use in Specific Populations (8.1)]*.

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

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 (certolizumab pegol) for injection is supplied as a sterile white, lyophilized powder in a single-dose vial for subcutaneous use. After reconstitution of the lyophilized powder with 1 mL Sterile Water for Injection, USP, the final concentration is 200 mg/mL with a deliverable volume of 1 mL (200 mg) and a pH of approximately 5.2. Each single-dose vial provides 200 mg certolizumab pegol, lactic acid (0.9 mg), polysorbate (0.1 mg), and sucrose (100 mg).

CIMZIA (certolizumab pegol) injection is supplied as a sterile, clear to opalescent, colorless to pale yellow solution that may contain particulates in a single-dose prefilled syringe for subcutaneous use. Each prefilled syringe delivers 1 mL of solution containing 200 mg certolizumab pegol, sodium acetate (1.36 mg), sodium chloride (7.31 mg), and Water for Injection, USP.

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, Crohn's disease, and plaque psoriasis 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 4.7 to 8 L in the population pharmacokinetic analysis for patients with Crohn's disease, patients with rheumatoid arthritis, and adult patients with plaque psoriasis.

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 clearance following subcutaneous dosing in patients with plaque psoriasis was 14 mL/h with an inter-subject variability of 22.2% (CV). 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. A population pharmacokinetic analysis was also conducted on data from patients with plaque psoriasis to evaluate the effect of age, gender, body weight, and presence of anti-certolizumab pegol antibodies. 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 $\geq$3 to 4-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 immunosuppressants.

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 3. 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 3: 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 4. 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 4: 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 5. 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 5: 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.

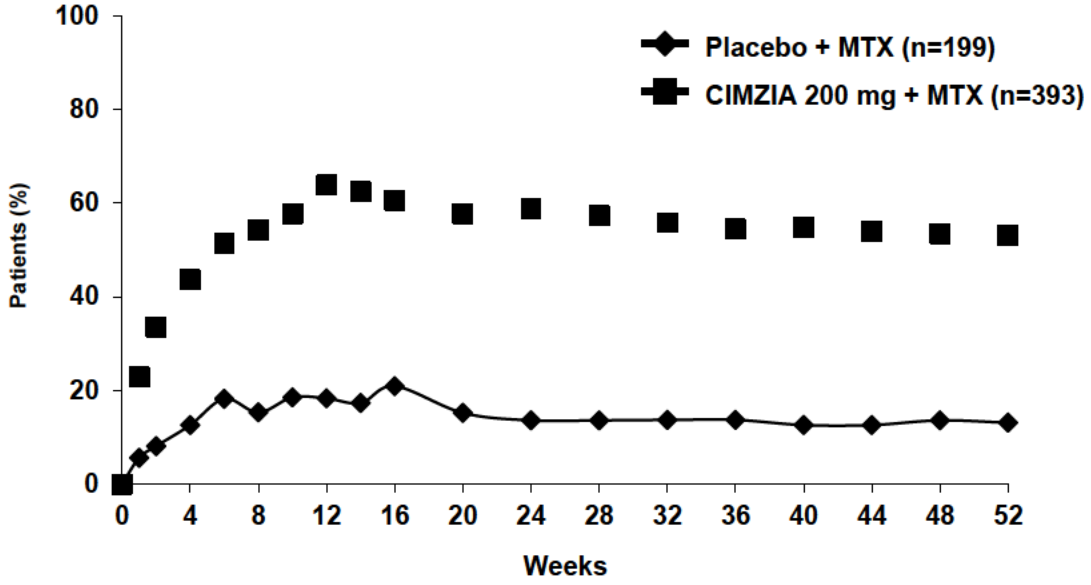
Table 6: Components of ACR Response in Studies RA-I and RA-IV

Parameter[+]	Study RA-I				Study RA-IV			
	Placebo + MTX N=199		CIMZIA[(a)] 200 mg + MTX q 2 weeks N=393		Placebo 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 7. 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 7: 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).

14.3 Psoriatic Arthritis

The efficacy and safety of CIMZIA were assessed in a multi-center, randomized, double-blind, placebo controlled trial (PsA001) in 409 patients aged 18 years and older with active psoriatic arthritis despite DMARD therapy. Patients in this study had ≥ 3 swollen and tender joints and adult-onset PsA of at least 6 months' duration as defined by the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria, and increased acute phase reactants. Patients had failed one or more DMARDs. Previous treatment with one anti-TNF biologic therapy was allowed, and 20% of patients had prior anti-TNF biologic exposure. Patients receiving concomitant NSAIDs and conventional DMARDs were 73% and 70 % respectively.

Patients received a loading dose of CIMZIA 400 mg at Weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either CIMZIA 200 mg every other week or CIMZIA 400 mg every 4 weeks or placebo every other week. Patients were evaluated for signs and symptoms and structural damage using the ACR20 response at Week 12 and modified Total Sharp Score (mTSS) at Week 24.

Clinical Response

The percentage of CIMZIA-treated patients achieving ACR20, 50 and 70 responses in study PsA001 are shown in Table 8. ACR20 response rates at weeks 12 and 24 were higher for each CIMZIA dose group relative to placebo (95% confidence intervals for CIMZIA 200 mg minus placebo at weeks 12 and 24 of (23%, 45%) and (30%, 51%), respectively and 95% confidence intervals for CIMZIA 400 mg

minus placebo at weeks 12 and 24 of (17%, 39%) and (22%, 44%), respectively). The results of the components of the ACR response criteria are shown in Table 9.

Patients with enthesitis at baseline were evaluated for mean improvement in Leeds Enthesitis Index (LEI). CIMZIA-treated patients receiving either 200 mg every 2 weeks or 400 mg every 4 weeks showed a reduction in enthesitis of 1.8 and 1.7, respectively as compared with a reduction in placebo-treated patients of 0.9 at week 12. Similar results were observed for this endpoint at week 24. Treatment with CIMZIA resulted in improvement in skin manifestations in patients with PsA.

Table 8: ACR Responses in Study PsA001 (Percent of Patients)

Response[c]	**Placebo N=136**	**CIMZIA[a] 200 mg Q2W N=138**	**CIMZIA[b] 400 mg Q4W N=135**
ACR20			
Week 12	24%	58%	52%
Week 24	24%	64%	56%
ACR50			
Week 12	11%	36%	33%
Week 24	13%	44%	40%
ACR70			
Week 12	3%	25%	13%
Week 24	4%	28%	24%

[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 preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
[c] Results are from the randomized set. Non-responder Imputation (NRI) is used for patients who escaped therapy or had missing data.

Table 9: Components of ACR Response in Study PsA001

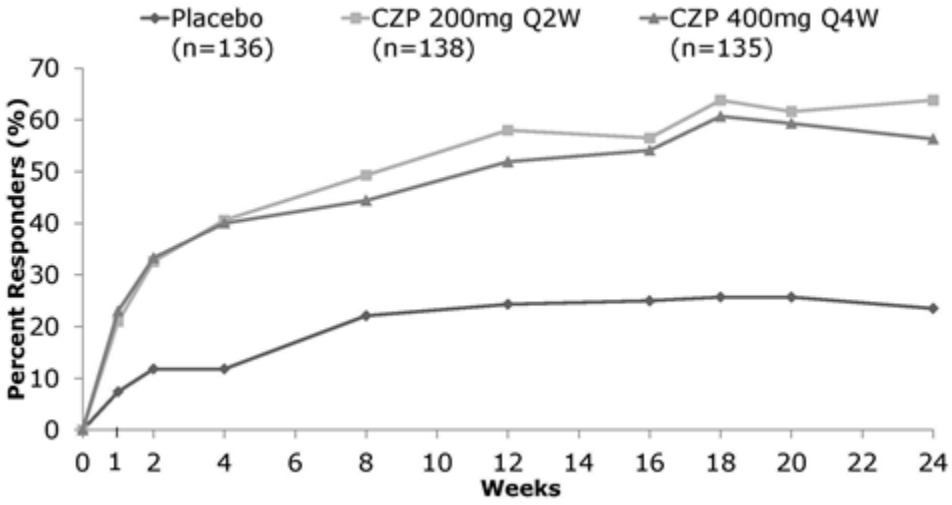
Parameter	**Placebo[c] N=136**		**CIMZIA[a] 200 mg Q2W N=138**		**CIMZIA[b] 400 mg Q4W N=135**	
	Baseline	**Week 12**	**Baseline**	**Week 12**	**Baseline**	**Week 12**
Number of tender joints (0-68)[d]	20	17	22	11	20	11
Number of swollen joints (0-66)[d]	10	9	11	4	11	5
Physician global assessment[d, e]	59	44	57	25	58	29
Patient global assessment[d, e]	57	50	60	33	60	40

Pain[(d, f)]	60	50	60	33	61	39
Disability index (HAQ)[(d, g)]	1.30	1.15	1.33	0.87	1.29	0.90
CRP (mg/L)	18.56	14.75	15.36	5.67	13.71	6.34

[(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 preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
[(c)] Results are from the entire placebo group
[(d)] Last Observation Carried Forward is used for missing data, early withdrawals or placebo escape
[(e)] Patient and Physician Global Assessment of Disease Activity, VAS 0=best 100= worst
[(f)] The Patient Assessment of Arthritis Pain, VAS 0=no pain and 100= most severe pain
[(g)] The HAQ-DI, 4 point scale 0=without difficulty and 3=unable to do
All values presented represent the mean
Results are from the randomized set (either with imputation or observed case)

The percent of patients achieving ACR20 responses by visit for PsA001 is shown in Figure 2.

Figure 2: Study PsA001-ACR20 Response Over 24 Weeks*



Randomized Set. Non-responder imputation used for patients with missing data or those who escaped therapy.
*The same patients may not have responded at each time point.

Radiographic Response

In study PsA001, 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 score (JSN) at week 24, compared to baseline. The mTSS score was modified for psoriatic arthritis by addition of hand distal interphalangeal (DIP) joints.

Patients treated with CIMZIA 200 mg every other week demonstrated greater reduction in radiographic progression compared with placebo-treated patients at Week 24 as measured by change from baseline in total modified mTSS Score (estimated mean score was 0.18 in the placebo group compared with -0.02 in the CIMZIA 200 mg group; 95% CI for the difference was (-0.38, -0.04)). Patients treated with CIMZIA

400 mg every four weeks did not demonstrate greater inhibition of radiographic progression compared with placebo-treated patients at Week 24.

Physical Function Response

In Study PsA001, CIMZIA-treated patients showed improvement in physical function as assessed by the Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 24 as compared to placebo (estimated mean change from baseline was 0.19 in the placebo group compared with 0.54 in the CIMZIA 200 mg group; 95% CI for the difference was (-0.47, -0.22) and 0.46 in the CIMZIA 400 mg group; 95% CI for the difference was (-0.39, -0.14)).

14.4 Ankylosing Spondylitis

The efficacy and safety of CIMZIA were assessed in one multicenter, randomized, double-blind, placebo-controlled study (AS-1) in 325 patients ≥18 years of age with adult-onset active axial spondyloarthritis for at least 3 months. The majority of patients in the study had active AS.

Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and spinal pain ≥4 on a 0 to 10 Numerical Rating Scale (NRS). Patients must have been intolerant to or had an inadequate response to at least one NSAID. Patients were treated with a loading dose of CIMZIA 400 mg at Weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either 200 mg of CIMZIA every 2 weeks or 400 mg of CIMZIA every 4 weeks or placebo. Concomitant NSAIDs were received by 91% of the AS patients. The primary efficacy variable was the proportion of patients achieving an ASAS20 response at Week 12.

Clinical Response

In study AS-1, at Week 12, a greater proportion of AS patients treated with CIMZIA 200 mg every 2 weeks or 400 mg every 4 weeks achieved ASAS 20 response compared to AS patients treated with placebo (Table 10). Responses were similar in patients receiving CIMZIA 200 mg every 2 weeks and CIMZIA 400 mg every 4 weeks. The results of the components of the ASAS response criteria and other measures of disease activity are shown in Table 11.

Table 10: ASAS Responses in AS patients at Weeks 12 and 24 in study AS-1

Parameters	Placebo N=57	CIMZIA[(a)] 200 mg every 2 weeks N=65	CIMZIA[(b)] 400 mg every 4 weeks N=56
ASAS20			
Week 12	37%	57%	64%
Week 24	33%	68%	70%
ASAS40			
Week 12	19%	40%	50%
Week 24	16%	48%	59%

[(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 preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
All percents reflect the proportion of patients who responded in the full analysis set

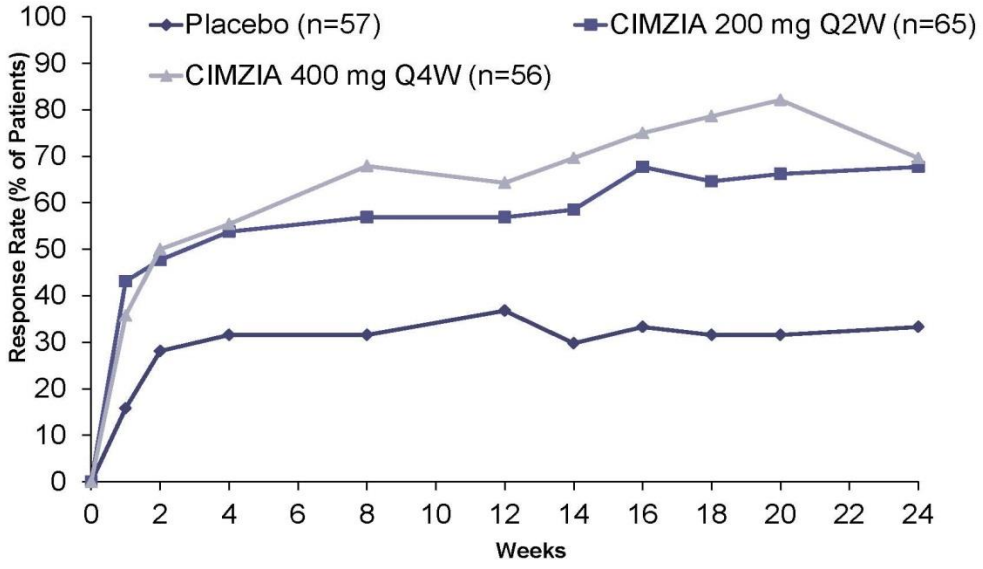
Table 11: Components of the ASAS response criteria and other measures of disease activity in AS patients at baseline and Week 12 in study AS-1

	Placebo N=57		CIMZIA[(a)] 200 mg every 2 weeks N=65		CIMZIA[(b)] 400 mg every 4 weeks N=56	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
ASAS20 response criteria						
-Patient Global Assessment (0-10)	6.9	5.6	7.3	4.2	6.8	3.8
-Total spinal pain (0-10)	7.3	5.8	7.0	4.3	6.9	4.0
-BASFI (0-10)[(c)]	6.0	5.2	5.6	3.8	5.7	3.8
-Inflammation (0-10)	6.7	5.5	6.7	3.8	6.4	3.4
BASDAI (0-10)[(d)]	6.4	5.4	6.5	4.0	6.2	3.7
BASMI [(e)]	4.8	4.4	4.2	3.6	4.3	3.9

[(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 preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
[(c)]BASFI is Bath Ankylosing Spondylitis Functional Index
[(d)]BASDAI is Bath Ankylosing Spondylitis Disease Activity Index
[(e)]BASMI is Bath Ankylosing Spondylitis Metrology Index
All values presented represent the mean in the full analysis set

The percent of AS patients achieving ASAS20 responses by visit for Study AS001 is shown in Figure 3. Among patients receiving CIMZIA, clinical responses were seen in some AS patients within one to two weeks after initiation of therapy.

Figure 3: Study AS-1: ASAS20 response over 24 weeks in AS patients *



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

14.5 Plaque Psoriasis

Three multicenter, randomized, double-blind studies (Study PS-1 [NCT02326298], Study PS-2 [NCT02326272], and Study PS-3 [NCT02346240]) enrolled subjects 18 years of age or older with moderate-to-severe plaque psoriasis who were eligible for systemic therapy or phototherapy. Subjects had a Physician Global Assessment (PGA) of ≥ 3 ("moderate") on a 5-category scale of overall disease severity, a Psoriasis Area and Severity Index (PASI) score ≥ 12, and body surface area (BSA) involvement of ≥ 10%.

Studies PS-1 (234 subjects) and PS-2 (227 subjects) randomized subjects to placebo, CIMZIA 200 mg every other week (following a loading dose of CIMZIA 400 mg at Weeks 0, 2, and 4), or CIMZIA 400 mg every other week. Studies PS-1 and PS-2 assessed the co-primary endpoints of the proportion of patients who achieved a PASI 75 and PGA of "clear" or "almost clear" with at least a 2-point improvement at Week 16. Other evaluated outcomes were PASI 90 at Week 16 and maintenance of efficacy to Week 48.

Study PS-3 randomized 559 subjects to receive placebo, CIMZIA 200 mg every other week (following a loading dose of CIMZIA 400 mg at Weeks 0, 2, and 4), CIMZIA 400 mg every other week up to Week 16, or a biologic comparator (up to Week 12). Study PS-3 assessed the proportion of patients who achieved a PASI 75 at Week 12 as the primary endpoint. Other evaluated outcomes were PGA of "clear" or "almost clear" at Week 16, PASI 75 at Week 16, PASI 90 at Week 16, and maintenance of efficacy to Week 48.

Of the 850 subjects randomized to receive placebo or CIMZIA in these placebo-controlled studies, 29% of patients were naïve to prior systemic therapy for the treatment of psoriasis, 47% had received prior phototherapy or chemophototherapy, and 30% had received prior biologic therapy for the treatment of psoriasis. Of the 850 subjects, 14% had received at least one TNF alpha agent and 16% had received an anti-IL agent. Eighteen percent of subjects reported a history of psoriatic arthritis at baseline.

Across all studies and treatment groups, the mean PASI score at baseline was 20 and ranged from 12 to 69. The baseline PGA score ranged from moderate (70%) to severe (30%). Mean baseline BSA was 25% and ranged from 10% to 96%. Subjects were predominantly men (64%) and White (94%), with a mean age of 46 years.

Clinical Response
Table 12 presents the efficacy results of PS-1, PS-2, and PS-3 at Week 16.

Table 12: Efficacy Results at Week 16 in Adults with Plaque Psoriasis in PS-1, PS-2, and PS-3 [MI[(a)]]

	Study PS-1			Study PS-2			Study PS-3[(e)]		
	Placebo (N=51)	CIMZIA 200mg[(c)] Q2W (N=95)	CIMZIA 400mg Q2W (N=88)	Placebo (N=49)	CIMZIA 200mg Q2W (N=91)	CIMZIA 400mg Q2W (N=87)	Placebo (N=57)	CIMZIA 200mg Q2W (N=165)	CIMZIA 400mg Q2W (N=167)
PGA of 0 or 1[(b, d)]	4%	45%	55%	3%	61%	65%	4%	52%	62%
PASI 75[(b)]	7%	65%	75%	13%	81%	82%	4%	69%	75%
PASI 90	0%	36%	44%	5%	50%	52%	0%	40%	49%

[(a)] Missing data was imputed using multiple imputation based on the MCMC method.
[(b)] The co-primary efficacy endpoints at Week 16 in PS-1 and PS-2.
[(c)] Subjects received 400 mg of CIMZIA at Weeks 0, 2, and 4, followed by 200 mg every other week.
[(d)] PGA score of 0 (clear) or 1 (almost clear).
[(e)] The primary endpoint in PS-3 was PASI 75 at Week 12.

Examination of age, gender, prior use of biologics, and prior use of systemic therapies did not identify difference in response to CIMZIA among these subgroups.

Based on a post-hoc subgroup analysis in subjects with moderate-to-severe psoriasis, stratified by ≤90 kg or >90 kg, subjects with both lower body weight and lower disease severity may achieve an acceptable response with CIMZIA 200 mg.

Maintenance of Response

In PS-1 and PS-2, among subjects who were PASI 75 responders at Week 16 and received CIMZIA 400 mg every other week, the PASI 75 response rates at Week 48 were 94% and 81%, respectively. In subjects who were PASI 75 responders at Week 16 and received CIMZIA 200 mg every other week, the PASI 75 response rates at Week 48 were 81% and 74%, respectively.

In PS-1 and PS-2, among subjects who were PGA clear or almost clear responders at Week 16 and received CIMZIA 400 mg every other week, the PGA response rates at Week 48 were 79% and 73%, respectively. In subjects who were PGA clear or almost clear responders at Week 16 and received CIMZIA 200 mg every other week, the PGA response rates at Week 48 were 79% and 76%, respectively.

In PS-3 study, subjects who achieved a PASI 75 response at Week 16 were re-randomized to either continue treatment with CIMZIA or be withdrawn from therapy (i.e., receive placebo). At Week 48, 98% of subjects who continued on CIMZIA 400 mg every other week were PASI 75 responders as compared to 36% of subjects who were re-randomized to placebo. Among PASI 75 responders at Week 16 who received CIMZIA 200 mg every other week and were re-randomized to either CIMZIA 200 mg every other week or placebo, there was also a higher percentage of PASI 75 responders at Week 48 in the CIMZIA group as compared to placebo (80% and 46%, respectively).

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 carton between 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

CIMZIA (certolizumab pegol) for injection is supplied as a sterile white, lyophilized powder in a single-dose vial for subcutaneous use.

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 needles (1 inch)
2	23 gauge needles (1 inch)
8	Alcohol swabs

Prefilled Syringe

NDC 50474-710-79

CIMZIA (certolizumab pegol) injection is supplied as a sterile, clear to opalescent, colorless to pale yellow solution in a single-dose prefilled syringe for subcutaneous use.

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.

Prefilled Syringe Starter Kit

NDC 50474-710-81

6 alcohol swabs and 6 single dose prefilled glass syringes with a fixed 25 ½ gauge thin-wall needle. The Starter Kit contains 3 sets of 2 prefilled syringes to provide sufficient drug supply for the initial 3 induction doses at the start of treatment. Each prefilled syringe contains 200 mg (1 mL) of CIMZIA.

When necessary, CIMZIA prefilled syringes may be stored at room temperature up to 77^{O}F (25^{O}C) in the original carton to protect from light for a single period of up to 7 days. Once a CIMZIA prefilled syringe has been stored at room temperature, do not place back in refrigerator. Write the date removed from the refrigerator in the space provided on the carton and discard if not used within the 7-day period.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

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 are not made with natural rubber latex.

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.

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to CIMZIA during pregnancy, patients can call 1-877-311-8972 *[see Use in Specific Populations 8.1]*.

Instruction on Prefilled Syringe Self-Injection Technique

After proper training by a qualified healthcare professional in subcutaneous injection technique, a patient may self-inject with CIMZIA using the Prefilled Syringe if a healthcare provider determines that it is appropriate. A patient's 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.

Full injection instructions are provided in the Instructions for Use booklet for the Prefilled Syringe, packaged in each CIMZIA Prefilled Syringe kit.

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.

Manufactured by:
UCB, Inc.
1950 Lake Park Drive
Smyrna, GA 30080

US License No. 1736

Medication Guide

CIMZIA® (CIM-zee-uh)

(certolizumab pegol)

lyophilized powder or solution for subcutaneous use

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

CIMZIA may cause serious side effects, including:

- **CIMZIA is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker** that can lower the ability of your immune system to fight infections. Some people who received CIMZIA have developed serious infections, including tuberculosis (TB) and infections caused by viruses, fungi, or bacteria that have spread throughout the body. Some of these serious infections have caused hospitalization and death.
  - Your healthcare provider should test you for TB before starting CIMZIA.
  - Your healthcare provider should monitor you closely for signs and symptoms of TB during treatment with CIMZIA.

  Before starting CIMZIA, tell your healthcare provider if you:
  - think you have an infection or have symptoms of an infection such as:
    - fever, sweat, or chills
    - cough
    - blood in phlegm
    - warm, red, or painful skin or sores on your body
    - burning when you urinate or urinate more often than normal
    - muscle aches
    - shortness of breath
    - weight loss
    - diarrhea or stomach pain
    - feeling very tired
  - are being treated for an infection
  - get a lot of infections or have infections that keep coming back
  - have diabetes, HIV-1 or a weak immune system. People with these conditions have a higher chance for infections.
  - have tuberculosis (TB), or have been in close contact with someone with TB
  - were born in, live, have lived, or traveled to certain countries where there is more risk for getting TB. Ask your healthcare provider if you are not sure.
  - live, have lived, or traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis). These infections may develop or become more severe if you receive CIMZIA. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.
  - have or have had hepatitis B
  - use the medicine Kineret (anakinra), Orencia® (abatacept), Rituxan® (rituximab), or Tysabri® (natalizumab)

  Stop using CIMZIA, and tell your healthcare provider right away if have any of the symptoms of an infection listed above.
- **Cancer.**
  - For people who receive TNF blockers, including CIMZIA, the chances of getting certain types of cancers may increase.
  - Some children, teenagers, and young adults who received TNF blockers, including CIMZIA, have developed lymphoma and other certain types of rare cancers, some of which have caused death. These cancers are not usually seen in this age group. **CIMZIA is not for use in children.**
  - People with inflammatory diseases including rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis, especially those with very active disease, may be more likely to get lymphoma.
  - Some people who receive TNF blockers, including CIMZIA, have developed a rare type of cancer which may cause death, called hepatosplenic T-cell lymphoma. Most of these people were male teenagers and young adult males with Crohn's disease or ulcerative colitis. Also, most of these people had been treated with both a TNF blocker and another medicine called IMURAN® (azathioprine) or PURINETHOL® (6-mercaptopurine, 6-MP).
  - Some people who receive CIMZIA, have developed certain types of skin cancer. Tell your healthcare provider if you develop any changes in the appearance of your skin, including growths on your skin, during or after treatment with

CIMZIA. You should see your healthcare provider periodically during treatment for skin examinations, especially if you have a history of skin cancer.

What is CIMZIA?

CIMZIA is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker used in adults 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)
- Treat active psoriatic arthritis (PsA)
- Treat active ankylosing spondylitis (AS)
- Treat moderate to severe plaque psoriasis (PsO) in adults who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills)

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

Before receiving CIMZIA, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection
- have or have had lymphoma or any other type of cancer
- have or had congestive heart failure
- have or have had seizures, any numbness or tingling, or a disease that affects your nervous system such as multiple sclerosis or Guillain-Barre syndrome.
- are scheduled to receive a vaccine. Do not receive a live vaccine while receiving CIMZIA.
- are allergic to certolizumab pegol or any of the ingredients in CIMZIA. See the end of this Medication Guide for a complete list of the ingredients in CIMZIA.
- are pregnant or plan to become pregnant. Tell your healthcare provider right away if you become pregnant during treatment with CIMZIA.

  Pregnancy Registry: If you become pregnant during treatment with CIMZIA, talk to your healthcare provider about registering in the pregnancy exposure registry for CIMZIA. You can enroll in this registry by calling 1-877-311-8972. The purpose of this registry is to collect information about the safety of CIMZIA during pregnancy.
- are breastfeeding or plan to breastfeed. Talk to your healthcare provider about the best way to feed your baby during treatment with CIMZIA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How will I receive CIMZIA?

- CIMZIA comes as lyophilized powder or as a solution in a prefilled syringe for injection.
- If your healthcare provider prescribes the CIMZIA powder, your CIMZIA should be injected by a healthcare provider. Each dose of CIMZIA will be given as 1 or 2 separate injections under the skin (subcutaneous injection) in your stomach area (abdomen) or upper thighs.

If your healthcare provider prescribes the CIMZIA prefilled syringe, you will be trained on how to inject CIMZIA.

- You will receive a **CIMZIA Prefilled Syringe Kit** including a complete **"Instructions for Use"** booklet for instructions on how to inject CIMZIA the right way.
- Read the detailed "Instructions for Use" for instructions about how to prepare and inject your dose of CIMZIA, and how to properly throw away used syringes containing the needle.
- Do not give yourself an injection of CIMZIA unless you have been shown by your healthcare provider. A family member

or friend can also be trained to help you give your injection. Talk to your healthcare provider if you have questions.

- CIMZIA prefilled syringe is given as an injection under the skin (subcutaneous injection) in your stomach area (abdomen) or upper thighs. Your healthcare provider will tell you how much and how often to inject CIMZIA. Do not use more CIMZIA or inject more often than prescribed.
- You may need more than 1 injection at a time depending on your prescribed dose of CIMZIA. If you are prescribed more than 1 injection, each injection should be given at a different site in your stomach or upper thighs.
- Make sure the solution in the CIMZIA prefilled syringe is clear and colorless to yellow and free from particles. **Do not use the CIMZIA prefilled syringe if the medicine is cloudy, discolored, or contains particles.**
- Do not miss any doses of CIMZIA. If you miss a dose, call your healthcare provider or pharmacist for instructions.
- Make sure to keep all follow-up appointments with your healthcare provider.

What are the possible side effects of CIMZIA?

CIMZIA can cause serious side effects, including:

- See **"What is the most important information I should know about CIMZIA?"**
- **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.
- **Allergic reactions.** Signs of an allergic reaction include a skin rash, swelling or itching of the face, tongue, lips, or throat, or trouble breathing.
- **Hepatitis B virus reactivation in people who carry the virus in their blood.** In some cases, people who received CIMZIA have died because of the hepatitis B virus being reactivated. Your healthcare provider should monitor you carefully before and during treatment with CIMZIA to see if you carry the hepatitis B virus in your blood. Tell your healthcare provider if you have any of the following symptoms:
  - feel unwell
  - tiredness (fatigue)
  - pain on the right side of your stomach (abdomen)
  - skin or eyes look yellow
  - poor appetite or vomiting
- **New or worsening nervous system problems, such as multiple sclerosis (MS), Guillain-Barre syndrome, seizures, or inflammation of the nerves of the eyes.** Symptoms may include:
  - dizziness
  - problems with your vision
  - numbness or tingling
  - weakness in your arms or legs
- **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 does not 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 healthcare provider right away if you have any serious side effects listed above.

The most common side effects of CIMZIA include upper respiratory infections (flu, cold), rash, urinary tract infections (bladder infections).

These are not all of the possible side effects of CIMZIA.

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

How should I store CIMZIA?

- Keep CIMZIA in the refrigerator between 36ºF to 46ºF (2ºC to 8ºC).
- Do not freeze CIMZIA.
- Protect CIMZIA from light**.** Store CIMZIA in the carton it came in.
- Do not use CIMZIA if the medicine is expired. Check the expiration date on the prefilled syringe or carton.
- The CIMZIA prefilled syringe is made of glass. Do not drop or crush the syringe.

Keep CIMZIA and all medicines out of the reach of children.

General information about the safe and effective use of CIMZIA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. 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 symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about CIMZIA that is written for health professionals.

What are the ingredients in CIMZIA?

CIMZIA lyophilized powder:
Active ingredient: certolizumab pegol
Inactive ingredients: lactic acid, polysorbate, sucrose
CIMZIA lyophilized powder is mixed with sterile Water for Injection.
CIMZIA prefilled syringe:
Active ingredient: certolizumab pegol
Inactive ingredients: sodium acetate, sodium chloride, Water for Injection
CIMZIA has no preservatives.

Product manufactured by:
UCB, Inc.
1950 Lake Park Drive
Smyrna, GA 30080
US License No. 1736

For more informa ion, go to www.CIMZIA.com or call 1-866-424-6942.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: May 2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Orig1s283

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number	125160/S-283
Priority or Standard	Standard
Submit Date	July 24, 2017
Received Date	July 24, 2017
PDUFA Goal Date	May 24, 2018
Division/Office	DDDP/ODE III
Review Completion Date	March 30, 2018
Established Name	certolizumab pegol
(Proposed) Trade Name	Cimzia®
Pharmacologic Class	Cimzia is TNF-α inhibitor
Code name	
Applicant	UCB Inc.
Formulation	Solution for injection
Dosing Regimen	400mg every 2 weeks administered by subcutaneous injection
Applicant Proposed Indication/Populations	For the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	CIMZIA is indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

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Reviewers Team and Signature Approval Section

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Nonclinical Reviewer	Jill Merrill, PhD	ODE III/DDDP	Sections 5, 13.4	**Select one:** ✓ Authored _____ Acknowledged _____ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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Clinical Reviewer	Melissa Reyes, MD, MPH, DTMH	ODE III/DDDP	Sections 1, 2, 3, 4, 5, 7.1, 7.3, 7.4, 7.5, 8, 9, 10, 11, 12, 13.1, and 13.2.	**Select one:** ✓ Authored _____ Acknowledged _____ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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Additional Reviewers of Application

Office/Division	Reviewer/Team Leader	Review Location
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OSE/DEPI	Patricia Bright, PhD, MSPH/ Sukhminder K. Sandhu, PhD, MPH, MS	DARRTS
OSE/PMS	Tri Bui-Nguyen, PhD/Darrell Lyons	Review not required

ADL = Associate Director of Labeling
DAPR2 = Division of Advertising and Promotion Review 2
DB III = Division of Biometrics III
DBRR I = Division of Biotechnology Research and Review 1
DCP 3 = Division of Clinical Pharmacology 3
DDDP = Division of Dermatology and Dental Products
DDS = Deputy Director for Safety
DEPI = Division of Epidemiology
DMPP = Division of Medical Policy
DPM = Division of Pharmacometrics
DPMH = Division of Pediatrics and Maternal Health
DARRTS = Document Archiving, Reporting, and Regulatory Tracking System
OB = Office of Biostatistics
OBP = Office of Biotechnology Products
OCP = Office of Clinical Pharmacology
ODE III = Office of Drug Evaluation III
ODE IV = Office of Drug Evaluation IV
OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OPRO = Office of Program and Regulatory Operations
OSE= Office of Surveillance and Epidemiology
PLT = Patient Labeling Team
PMS = Project Management Staff
RBPMBI = Regulatory and Business Process Management Branch I
SRPM = Safety Regulatory Project Manager

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ANCOVA	analysis of covariance
ARIA	active risk identification and analysis system
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	body surface area
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHF	congestive heart failure
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CV	cardiovascular
DDDP	Division of Dermatology and Dental Products
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDF	financial disclosure form
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
ICU	intensive care unit
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISR	injection site reaction
ISS	integrated summary of safety
ITT	intent to treat
LLN	lower limit of normal

LOCF	last observation carried forward
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MS	multiple sclerosis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NYHA	New York Heart Association
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamics
PEG	pegol
PeRC	Pediatric Review Committee
PGA	Physician's Global Assessment
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PPS	per protocol set
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
RBC	red blood cells
REMS	risk evaluation and mitigation strategy
RS	randomized set
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SMQ	standard MedDRA query
SOC	system organ class
sub yrs	subject years
TEAE	treatment emergent adverse event
ULN	upper limit of normal
URTI	upper respiratory tract infection
WBC	white blood cells

1 Executive Summary

1.1. Product Introduction

CIMZIA (certolizumab pegol) injection for subcutaneous injection is a humanized antigen-binding antibody fragment (Fab') conjugated to polyethylene glycol (PEG) that selectively binds and neutralizes membrane-associated and soluble TNFα. TNFα is a naturally occurring cytokine that is involved in inflammatory and immune responses. Certolizumab pegol (certolizumab) inhibits the release of pro-inflammatory cytokines and chemokines including those implicated in the pathogenesis of psoriasis. The addition of PEG to the structure increases the half-life of the molecule to 14 days, while the lack of Fc (fragment crystallizable) region prevents certolizumab from fixing complement or inducing antibody-dependent cell-mediated cytotoxicity *in vitro*.

Certolizumab is approved for the following indications:

- 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
- Treatment of adults with moderately to severely active rheumatoid arthritis
- Treatment of adult patients with active psoriatic arthritis
- Treatment of adults with active ankylosing spondylitis

The proposed indication is treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The proposed dose is 400mg every other week administered by subcutaneous injection. The proposed commercial presentation for certolizumab drug product is (200mg/mL) is a single use pre-filled syringe (PFS) with a 1 mL deliverable volume as well as a 200mg lyophilized powder in a single-dose vial.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant submitted data from three adequate and well-controlled trials Trial PS0005 (CIMPASI 1), Trial PS0002 (CIMPASI 2), and Trial PS0003 (CIMPACT), which provided evidence of the effectiveness of certolizumab for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Trials PS0005 and PS0002 assessed the changes from baseline to Week 16 compared to placebo for the two co-primary endpoints:

- the proportion of subjects who achieved an Investigator's Global Assessment (IGA) score of 0 ("clear") or 1 ("almost clear")
- the proportion of subjects who achieved at least a 75% reduction in the Psoriasis Area and Severity Index (PASI) composite score (PASI 75)

Trial PS0003 assessed the change from baseline to Week 12 compared to placebo for the primary endpoint of proportion of subjects achieving PASI 75.

Certolizumab was statistically superior to placebo (p-values <0.001) on the co-primary endpoints in Trials PS0005 and PS0002 and on the primary endpoint in Trial PS0003. The applicant has demonstrated that certolizumab is effective for its intended use in the target population, and has met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Psoriasis is a chronic, inflammatory disease that primarily affects the skin and is characterized by erythematous, scaly plaques and substantial impairment of quality of life. CIMZIA (certolizumab pegol) injection, for subcutaneous use is proposed for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Certolizumab pegol, the active ingredient in CIMZIA, is approved for several inflammatory conditions. Certolizumab pegol (certolizumab) is a humanized antigen-binding antibody fragment (Fab') conjugated to polyethylene glycol (PEG) that selectively binds and neutralizes membrane-associated and soluble TNFα. TNFα is a naturally occurring cytokine that is involved in inflammatory and immune responses. Certolizumab inhibits the release of pro-inflammatory cytokines and chemokines including those implicated in the pathogenesis of psoriasis. Certolizumab 200mg is available as a single use pre-filled syringe (PFS) as well as a 200mg lyophilized powder in a single-dose vial.

For the treatment of moderate to severe plaque psoriasis, current therapeutic options include phototherapy and photochemotherapy with methoxsalen, systemic small molecule drugs (acitretin, apremilast, cyclosporine, methotrexate), and biologic products (adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab and brodalumab). Although the efficacy varies, no product produces a response in all patients or provides a permanent cure. Phototherapy and photochemotherapy may be impractical due to office-based administration requirements. All of the systemic products have one or more possible serious adverse reactions associated with their use, including malignancy, serious infections, teratogenicity, depression, nephrotoxicity, hepatotoxicity, and bone marrow suppression.[1] Because of these limitations, there is a recognizable need for additional therapeutic options despite the number of available therapies.

Substantial efficacy was demonstrated in three pivotal trials. Trial PS0005, PS0002, and Trial PS0003 enrolled 1020 adult subjects with moderate to severe plaque psoriasis who were eligible for systemic therapy or phototherapy. Subjects had an Investigator's Global Assessment (IGA) score of ≥3 ("moderate") on a 5-point scale of overall disease severity, a Psoriasis Area and Severity Index (PASI) score ≥12, and a minimum affected body surface area (BSA) involvement of ≥10%. In PS0005 and PS0002, subjects were randomized to either certolizumab (400mg Week 0, 2, and 4 followed by 200mg every 2 weeks, or 400mg every 2 weeks), or placebo. In PS0003, subjects were randomized to either certolizumab (400mg Week 0, 2, and 4 followed by 200mg every 2 weeks or 400mg every 2 weeks) or placebo, or etanercept (50mg twice weekly). The applicant is not seeking a comparative claim to etanercept.

In PS0005 and PS0002, the co-primary endpoints were i) the proportion of subjects who achieved an IGA score of 0 ("clear") or 1 ("almost clear"), and ii) the proportion of subjects who achieved at least a 75% reduction in the PASI composite score (PASI 75), both assessed at Week 16. In PS0003, primary endpoint was PASI 75 at Week 12. In Trials PS0005 and PS0002, certolizumab was superior to placebo on both IGA for

[1] Menter A et al. Guidelines of care for the management of psoriasis and psoriatic arthritis Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008;58:826-50.

both doses (Trial PS0005: 400mg-55 %, 200mg-45% vs 4% and Trial PS0002: 400mg-65%, 200mg-61% vs3%) and PASI 75 (Trial PS0005: 400mg-75%, 200mg-65% vs 7% and Trial PS0002: 400mg-82%, 200mg-81% vs 13%) at Week 16. In Trial PS0003, certolizumab was superior to placebo on PASI 75 at Week 12 (400mg-75%, 200mg-69% vs 4%).

In Trials PS0005 and PS0002, to evaluate maintenance and durability of response, subjects randomized to certolizumab at Week 0 and who were PASI75 responders at Week 16 were continued on the same treatment. For subjects who were responders and received certolizumab 400mg, the maintenance response rate at Week 48 for PS0005 and PS0002 was 94% and 81%, respectively. For subjects who were responders and received certolizumab 200mg, the maintenance response rate at Week 48 for PS0005 and PS0002 was 81% and 74%, respectively. In Trial PS0003, subjects who were PASI75 responders at Week 16 were randomized to continue treatment or withdrawn from treatment (placebo). Of subjects re-randomized to certolizumab 400mg or placebo, 98% of subjects continued on certolizumab 400mg maintained PASI75 compared to 36% of subjects who received placebo. Of subjects re-randomized to certolizumab 200mg or placebo, 80% of subjects continued on certolizumab 200mg maintained PASI75 compared to 46% of subjects who received placebo.

The primary safety database, which consisted of data from the pooled Phase 3 Trials PS0005, PS0002, and PS0003 was adequate to characterize the safety profile of CIMZIA (certolizumab) injection. Based on the analysis of the submitted data, treatment with certolizumab did not appear to increase the risk of mortality. The majority of serious adverse events (SAEs) were single events with no identifiable pattern. Two subjects discontinued study drug due to SAE of infection during the placebo-controlled period of the pivotal trials (abdominal abscess) and Phase 2 trial (disseminated tuberculosis). Analysis of expected adverse reactions based on biologic plausibility and potential class effects did not identify a safety signal. Treatment with certolizumab was not associated with an increased incidence of major adverse cardiovascular events (MACE). One case of disseminated tuberculosis occurred during Phase 2. No adverse event of congestive heart failure, cytopenia, or lupus-like syndrome occurred during the placebo-controlled period of Phase 2 and 3 studies. No adverse events of demyelinating disease occurred during the placebo-controlled period of Phase 2 and 3 studies, while 2 subjects experienced adverse events of multiple sclerosis, including one subject with a history of falls and gait disturbance 2 years prior to trial participation. One serious hypersensitivity reaction was reported in subjects treated with certolizumab during the Phase 3 trials (anaphylactoid reaction). However, infections such as upper respiratory infections and herpes simplex (HSV) infections occurred more frequently in subjects treated with certolizumab compared to subjects treated with placebo. All AEs were mild to moderate in severity and did not lead to discontinuation of certolizumab. In addition, elevated liver enzymes were reported more frequently in the certolizumab group (400mg - 2.3%, 200mg - 4.3%) than the placebo group (2.5%). In the certolizumab group, elevated liver enzymes led to study discontinuation for 2 subjects. Adverse reactions, occurring in ≥ 1% and observed more frequently in subjects receiving certolizumab through Week 16, were: headache, injection site reactions, and cough.

Prescription and patient labeling, including a Medication Guide, as well as pharmacovigilance are adequate to manage the risk of CIMZIA in the postmarketing milieu; a Risk Evaluation and Mitigation Strategy (REMS) is not needed. Recommended postmarketing requirements under 505(o) are:

- a prospective registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to certolizumab during pregnancy to an unexposed control population.

- a retrospective cohort study to assess adverse pregnancy outcomes
- enhanced pharmacovigilance to assess for malignancy and other serious adverse reactions
- required pediatric assessment, Pediatric Research Equity Act (PREA) (21 U.S.C. 355c): a safety, efficacy and PK study in pediatric subjects 6 years to < 18 years of age with moderate to severe plaque psoriasis.

The available safety and efficacy data supports the approval of CIMZIA (certolizumab) injection for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Although there are a number of FDA-approved products with an acceptable risk-benefit profile for this indication, none of these treatments provides a permanent cure or universal response and all of these products are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is still a need for additional therapeutic options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Psoriasis is a common, chronic, inflammatory multi-system disorder, which primarily affects the skin and joints and is associated with substantial impairment of quality of life. The prevalence of psoriasis in the US is approximately 2-3%, of which an estimated 20% have moderate to- severe disease. One third of patients have concomitant arthritis. Other comorbidities include depression/suicide, autoimmune disease, cardiovascular disease, and metabolic syndrome.[1]	Moderate to severe plaque psoriasis is a serious disease because of its chronicity, impact on quality of life, and co-morbidities.
Current Treatment Options	• FDA approved drugs for the treatment of moderate to severe psoriasis include anti-metabolites (methotrexate), tumor necrosis factor (TNF) inhibitors (etanercept, adalimumab and infliximab), IL-12/23 blockers (ustekinumab, guselkumab, and tildrakizumab), IL-17A blockers (secukinumab and ixekizumab), IL-17A receptor antagonist (brodalumab), T cell inhibitor (cyclosporine), retinoids (acitretin), and phosphodiesterase 4 inhibitors (apremilast). Other treatment options include phototherapy with either PUVA (UVA light combined with methoxsalen) or UVB light (narrow or broadband). • All approved therapeutic options may be associated with the risk of serious adverse reactions or administration challenges. The use of phototherapy and photochemotherapy are limited by the need for office administration and additional photoprotection. Teratogenicity and hyperlipidemia are labeled risks with acitretin. Depression and weight loss are safety concerns with apremilast. The primary risks of cyclosporine use are nephrotoxicity and hypertension. Methotrexate has teratogenic, hepatotoxic, nephrotoxic effects, and may cause bone marrow toxicity and pulmonary fibrosis. Other systemic products may cause immunosuppression, serious infections, and malignancy. All biologic products may be associated with loss of effect and serious hypersensitivity reactions. See the Summary of Treatment Armamentarium for Moderate to Severe Psoriasis for the specific labeled safety issues for each product.	There are a number of FDA-approved products with an acceptable risk-benefit profile for the treatment of moderate-to severe plaque psoriasis in adults. None of these treatments provides a permanent cure or universal response and all of these products are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Data from Trials PS0005, PS0002, and PS0003 provided substantial evidence of the effectiveness of certolizumab for the treatment of moderate to severe plaque psoriasis. These trials enrolled 1020 adult subjects with moderate to severe plaque psoriasis defined as Investigator's Global Assessment (IGA) score of ≥3 ("moderate") on a 5-point scale of overall disease severity, a Psoriasis Area and Severity Index (PASI) score ≥12, and a minimum affected body surface area (BSA) involvement of ≥10%. In all three trials, subjects were randomized to either certolizumab (400mg every other week), certolizumab 400mg Week 0, 2, and 4 followed by 200mg every other week, or placebo. The co-primary endpoints were i) the proportion of subjects who achieved an IGA score of 0 ("clear") or 1 ("almost clear"), and ii) the proportion of subjects who achieved at least a 75% reduction in the PASI composite score (PASI 75), both assessed at Week 16 in Trial PS0005 and PS0002 and at Week 12 in Trial PS0003. • In Trials PS0005 and PS0002, certolizumab was superior to placebo on both IGA for both doses (Trial PS0005: 400mg-55 %, 200mg-45% vs 4% and Trial PS0002: 400mg-65%, 200mg-61% vs3%) and PASI 75 (Trial PS0005: 400mg-75%, 200mg-65% vs 7% and Trial PS0002: 400mg-82%, 200mg-81% vs 13%) at Week 16. In Trial PS0003, certolizumab was superior to placebo on PASI 75 at Week 12 (400mg-75%, 200mg-69% vs 4%).	The data submitted by the applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled. The results are persuasive. Achievement of clear or almost-clear skin is an intrinsically meaningful outcome for a cutaneous disease such as psoriasis. The data suggest that a patient with moderate to severe plaque psoriasis treated with 400mg certolizumab every 2 weeks is likely to achieve clear or almost clear skin by Week 16, and to maintain this effect with continued treatment to Week 48.
Risk		The safety profile of certolizumab has been adequately characterized. At this time, the safety profile appears to be similar to the other TNF inhibitors. In view of the premarket safety database for certolizumab in subjects with psoriasis, and postmarket data for the approved indications, it is unlikely that postmarketing exposure will identify additional

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		risks for malignancy or specific organ toxicities in patients with psoriasis of a magnitude that would alter the risk-benefit conclusion.
Risk Management	• The following PMRs and PMCs are recommended: PMR 3408-1 Conduct a Pharmacokinetics (PK), Safety, and Efficacy Study in pediatric subjects 6 to less than 18 years of age with moderate to severe psoriasis (with a duration of exposure to certolizumab pegol of at least one year). PMR 3408-2 Utilize the validated immunogenicity assays developed under PMC 3408-5 and PMC 3408-6 to analyze the immunogenicity profile of certolizumab pegol using banked patient samples from Phase 3 trials CIMPASI-1, CIMPASI-2, and CIMPACT. Evaluate the impact of immunogenicity on pharmacokinetics, efficacy, and safety in subjects with psoriasis based on the immunogenicity data generated with the newly validated assays. PMR 3408-3 A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to certolizumab pegol during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, will be assessed through at least the first year of life. You	Prescription labeling, patient labeling (including Medication Guide), and routine pharmacovigilance, in conjunction with the post marketing requirements, are adequate to manage the risks of the product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	may expand a current prospective registry to include women who are exposed to certolizumab pegol for the treatment of plaque psoriasis. PMR 3408-4 Conduct a retrospective cohort study using claims or electronic medical record data or a case control study to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths, and infant infections in women exposed to certolizumab pegol during pregnancy compared to an unexposed control population. PMC 3408-5 Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to certolizumab pegol, including procedures for the accurate detection of binding antibodies to certolizumab pegol in the presence of certolizumab pegol levels expected in the serum or plasma at the time of patient sampling. In addition, an assessment of the contribution of binding antibodies to PEG should also be evaluated. PMC 3408-6 Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to certolizumab pegol, including procedures for the accurate detection of neutralizing antibodies to certolizumab pegol in the presence of certolizumab pegol levels that are expected in the serum or plasma at the time of patient sampling. • Labeling: Prescription labeling adequately addresses the risks identified during product development and conveys the lack of data from human exposure during pregnancy. A Medication Guide and Instructions for Use for the proposed presentation are included in patient labeling and are appropriate to inform patients of potential	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	risks. • A REMS is not recommended. Precedent biologic products with comparable safety profiles have a similar approach to post-marketing risk management.	

2 Therapeutic Context

Analysis of Condition

Psoriasis is a common, chronic, immune-mediated skin disorder. The characteristic lesion is a sharply demarcated erythematous plaque with micaceous scale, and the plaques may be localized or widespread in distribution.[2] Psoriasis is a complex autoimmune inflammatory disease that occurs in genetically susceptible individuals. The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, which produce proinflammatory cytokines, which trigger and perpetuate the inflammatory cascade.[3]

In the US and Canada, prevalences as high as 4.6% and 4.7% have been reported, respectively.[2] It is estimated that approximately 7.5 million people in the United States have psoriasis. Approximately 80 percent of those affected with psoriasis have mild to moderate disease, while 20 percent have moderate to severe psoriasis affecting more than 5 percent of the body surface area. The most common form of psoriasis is plaque psoriasis, affecting about 80 to 90 percent of psoriasis patients.[4]

Psoriasis can first appear at any age, from infancy to the eighth decade of life. Two peaks in age of onset have been reported: one at 20–30 years of age and a second peak at 50–60 years. In approximately 75% of patients, the onset is before the age of 40 years, and in 35–50%, it is before the age of 20 years. The age of onset is earlier in women than in men.[2]

The natural history of psoriasis is chronic with intermittent remissions. Although plaque psoriasis is the most common presentation, other forms of psoriasis include guttate, pustular, erythrodermic, and inverse psoriasis. Psoriasis may affect fingernails and toenails, most frequently in association with psoriatic arthritis. A diagnosis of psoriasis can be made by history and physical examination in the vast majority of cases. The differential diagnosis of psoriasis may include seborrheic dermatitis, lichen simplex chronicus, atopic dermatitis, and nummular eczema. Occasionally, a skin biopsy is performed to rule out other conditions.[2]

The presentation of psoriasis in the pediatric population can be different from that in adults. Psoriasis in infants often presents with involvement of the diaper area. Infants with diaper-area involvement typically develop symmetrical, well-demarcated erythematous patches with little scale. Maceration may be present. Unlike irritant diaper dermatitis, the inguinal folds are usually involved. Affected infants may also have

[2] Feldman, Steven R., MD. PhD; Epidemiology, Clinical Manifestations, and Diagnosis of Psoriasis; UpToDate.com; updated December 9, 2015
[3] Blauvelt, Andrew and Ehst, Benjamin D, Pathophysiology of Psoriasis; UpToDate.com; updated July 8, 2015
[4] Menter A, Gottlieb A, Feldman SR, Van Voorhees AS et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008 May;58(5):826-50.

psoriatic plaques in other body areas. These plaques are often smaller and thinner than the psoriatic plaques in adult patients. In children, scalp involvement is a common and often initial presentation of chronic plaque psoriasis. In addition, children with chronic plaque psoriasis are more likely to have facial involvement than adults.[2]

A number of comorbid systemic conditions occur more frequently in patients with psoriasis. Examples of these conditions include cardiovascular disease, malignancy, diabetes, hypertension, metabolic syndrome, inflammatory bowel disease, serious infections, and autoimmune disorders. Psychiatric comorbidities associated with psoriasis include depression and suicidal ideation; neurotic, stress-related, or somatoform disorders; and personality and behavioral disorders.[5]

The impact of psoriasis on the daily lives of patients was among the topics discussed at a Patient-Focused Drug Development Meeting for psoriasis held by the Agency on March 17, 2016. Patients who attended the meeting described severe physical, social, and emotional impact including depression, anxiety, limitations on activities, embarrassment, stigma, and social discrimination. Patients shared their experiences with currently available therapies, and they described varying degrees of success in managing symptoms with these therapies. Patients stressed the need to enhance the treatment armamentarium, given current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments.

Psoriasis is a chronic, debilitating disease with significant impacts on the lives of affected patients. At the Patient Focused Drug Development meeting, patients discussed current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments. Therefore, development of additional safe and effective therapies continues to be an important goal. This is especially true for certain subgroups of patients with psoriasis, such as women during pregnancy and pediatric patients.

2.2. Analysis of Current Treatment Options

Although there are multiple topical therapies available for the treatment of psoriasis, topical therapies are not typically used alone for the treatment of moderate to severe disease. Approved systemic therapies for the treatment of moderate to severe plaque psoriasis are described in the table below.

[5] Korman, Neil; Comorbid Disease in Psoriasis; UpToDate.com; updated March 24, 2017.

Table 1: Summary of Treatment Armamentarium for Moderate to Severe Psoriasis

Product (s) Name/year approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments					
Antimetabolite/ Immunosuppressant					
Methotrexate 1972	Severe, recalcitrant, disabling, psoriasis not adequately responsive to other forms of therapy; *but only when diagnosis established, by biopsy and/or dermatologic consultation.* Must rule out undiagnosed concomitant disease affecting immune responses.	Starting Dose Schedules 1. Weekly single oral, intramuscular (IM) or intravenous (IV) dose schedule: 10 to 25 mg per week until adequate response is achieved. 2. Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses. 30 mg/wk should not ordinarily be exceeded.	No efficacy information for psoriasis in the label.	Boxed Warning (BW)- potentially fatal toxic reactions including bone marrow suppression, aplastic anemia, and gastrointestinal toxicity with concomitant NSAID[6] Tx; hepatotoxicity, pulmonary toxicity, kidney toxicity, opportunistic infections, malignant lymphoma, tumor lysis syndrome, severe skin toxicity, fetal death and anomalies "should not be used in pregnant women with psoriasis"	Major AE derm dosing: ↑Liver enzymes stomatitis, diarrhea, nausea and vomiting, lymphoprolifer ative disorders; Recommend Periodic liver biopsy if tx long-term Pregnancy: X
Tumor Necrosis Factor Inhibitors					
Infliximab (Remicade) 2006	Chronic severe (extensive or disabling) plaque psoriasis, candidates for phototherapy or systemic therapy and when other systemic therapies are medically less appropriate.	5 mg/kg IV at 0, 2 and 6 weeks, then every 8 weeks	From the label: 3 R, DB, PC[7] trials PASI75 at week 10 1-Inflix[8] (5mg/kg)- 80% vs 3% placebo 2- Inflix (5mg/kg)- 75% vs 2% placebo 3- Inflix (5mg/kg)- 88% vs Inflix (3mg/kg) 72% vs 6% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), malignancies including Hepatosplenic T-cell lymphomas (adolescents and young adults) Warnings: Hep B reactivation, heart failure, hepatotoxicity, cytopenias, hypersensitivity events, malignancy	Pregnancy: B

[6] Non-steroidal anti-inflammatory drug
[7] R=randomized, DB=double-blind, PC= placebo-controlled
[8] Inflix=infliximab

Product (s) Name/year approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Adalimumab (Humira) 2008	Moderate to severe chronic plaque psoriasis, candidates for phototherapy or systemic therapy	80 mg via subcutaneous injection (SC) initial dose, followed by 40 mg SC every other week starting one week after initial dose	From the label: 2 R, DB, PC[5] trials PASI75 at week 16 1-Ada[9]-71% vs 7% placebo 2- Ada-78% vs 19% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), malignancy including hepatosplenic T-cell lymphoma Warnings: hypersensitivity reactions, Hep B reactivation, demyelinating disease, cytopenias, heart failure, Lupus-like syndrome	Pregnancy: B
Etanercept (Enbrel) 2004; 2016	Chronic moderate to severe psoriasis, candidates for photo- therapy or systemic therapy; 11/2016- approved for patients 4 years of age and older	50 mg SC twice weekly for 3 months, followed by 50 mg once weekly; <63 kg (138 lb.)- 0.8 mg/kg SC weekly	From the label: 2 R, DB, PC5 trials PASI75 at 3 months 1-Etan[10]-47% vs 4% placebo 2-Etan-46% vs 3% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), lymphomas, other malignancies Warnings: demyelinating disease, worsen CHF, pancytopenia, malignancy, Hep B reactivation	Pregnancy: B
IL-12 and IL-23 blocker					
Ustekinumab (Stelara) 2009	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	For patients weighing <100 kg :45 mg SC initially and 4 weeks later, followed by 45 mg SC every 12 weeks For patients weighing >100 kg: 90 mg SC initially and 4 weeks later, followed by 90 mg SC every 12 weeks	From the label: 2 R, DB, PC trials PASI75 at week 12 1-uste[11](90mg)-66% vs uste(45mg)-67% vs 3% placebo 2-uste (90mg)-76% vs uste(45mg)-67% vs 4% placebo	Warnings and Precautions (W&Ps): Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, malignancy, reversible posterior leukoencephalopathy syndrome, pretreatment eval for TB.	Pregnancy: B
IL- 17A blocker					

[9] Ada=adalimumab
[10] Etan= etanercept
[11] Uste=ustekinumab

Product (s) Name/year approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Secukinumab (Cosentyx) 2015	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	300mg SC at Weeks 0, 1, 2, 3 and 4 followed by 300mg SC every 4 weeks. For some patients, a dose of 150 mg may be acceptable	From the label: 4 R, DB, PC trials PASI75 at week 12 1-sec[12] (300mg)-82% vs sec (150mg)-71% vs 4% placebo 2-sec (300mg)-76% vs sec (150mg)-67% vs 5% placebo 3-sec (300mg)-75% vs sec (150mg)-69% vs 0% placebo 4-sec (300mg)-87% vs sec (150mg)-70% vs 3% placebo	W&Ps: Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, Crohn's disease, hypersensitivity reactions, pretreatment eval for TB.	Pregnancy: B
Ixekizumab (Taltz) 2016	Moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	160 mg (two 80 mg injections) SC at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks	From the label: 3 R, DB, PC trials PASI75 at Week 12 1: Ixe[13] (80 mg q2wk) 89% vs 4% placebo 2: Ixe (80 mg q2wk) 90% vs 2% placebo 3: Ixe (160 mg x 1, then 80 mg q2wk) 87% vs 7% placebo	W&Ps: Infections (Upper respiratory tract, oral candidiasis, conjunctivitis and tinea infections; Inflammatory Bowel Disease (Crohn's disease and ulcerative colitis); hypersensitivity reactions; pretreatment eval for TB.	
IL- 17 Receptor A antagonist					
Brodalumab (Siliq) 2017	Moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies	210 mg by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks	From the Label: 3 R, DB, PC trials PASI 75 and sPGA of 0 ("clear") or 1 ("almost clear") at Week 12 1: Bro[14] (210 mg q2wk) PASI 75 83% vs 3% placebo; sPGA 0 or 1 Bro 76% vs 1% placebo 2: Bro (210 mg q2wk) PASI 75 86% vs 8% placebo; sPGA 0 or 1 Bro 79% vs 4% placebo; PASI 100 Bro 44% vs Uste 22%	Box warning for Suicidal Ideation and Behavior W&Ps: Suicidal ideation and behavior, Infections (serious infections and fungal infections), Crohn's disease, pretreatment eval for TB, and avoid live vaccines.	REMS requires prescribers and pharmacies to be certified; patients must sign a Patient-Prescriber agreement form

[12] Sec= secukinumab
[13] Ixe= Ixekizumab
[14] Bro= Brodalumab

Product (s) Name/year approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
			3: Bro (210 mg q2wk) PASI 75 85% vs 6% placebo; sPGA 0 or 1 Bro 80% vs 4% placebo; PASI 100 Bro 37% vs Uste 19%		
IL-23 blocker					
Guselkumab (Tremfya) 2017	Moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	100mg by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter	From the Label: 3 R, DB, PC, AC[15] trials; 1 & 2: PASI 90 and sPGA of 0 ("cleared") or 1 ("minimal") at Week 16 1: Gus[16] (100mg wk 0 &4 then q8wk) PASI 90 73% vs 3% placebo; IGA 0 or 1 85% vs 7% placebo 2: Gus (100mg wk 0 &4 then q8wk) PASI 90 70% vs 2% placebo; IGA 0 or 1 84% vs 8% placebo 3: Subjects began tx with Uste; at wk16 subjects with IGA ≥2 R to Gus or continued Uste; endpoint at wk 28 IGA 0 or 1 with ≥2 grade improvement; Gus 31% vs 14% Uste	W&Ps: Infections (upper respiratory tract infections, gastroenteritis, tinea infections, and herpes simplex infections), pretreatment eval for TB, avoid live vaccines.	
Tildrakizumab (Ilumya) 2018	Moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	100mg by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter	From the Label: 2 R, DB, PC trials; 1 & 2: PASI 75 and PGA of 0 ("cleared") or 1 ("minimal") at Week 12 1: Tild[17] PASI 75 64% vs 6% placebo; IGA 0 or 1 58% vs 7% placebo 2: Tild PASI 75 61%	W&Ps: Infections (upper respiratory tract infections), pretreatment eval for TB, avoid live vaccines.	

[15] AC= Active comparator
[16] Gus= Guselkumab
[17] Tild=Tildrakizumab

Product (s) Name/year approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
			vs 6% placebo; IGA 0 or 1 55% vs 4% placebo		
T-Cell Inhibitor/ Immunosuppressant					
Cyclosporine 1997	Adult, non-immunocompromised patients with severe recalcitrant disabling psoriasis who have failed at least one systemic therapy	Starting dose: 2.5 mg/kg/day, taken twice daily, dosage ↑ by 0.5 mg/kg/day at 2-week intervals, to a maximum of 4.0 mg/kg/day.	From the label: PASI75 - 51% at 8 weeks, 79% at 16 weeks	BW-Should only be used by MDs experienced in management of systemic immunosuppressive Rx, ↑ susceptibility to infections and development of neoplasia including lymphoma, also hypertension, nephrotoxicity which ↑ with ↑ doses. In psoriasis patients with history of PUVA, UVB, coal tar or radiation Rx- ↑ risk of skin malignancies Warnings: Hepatotoxicity, hyperkalemia, thrombotic microangiopathy, progressive multifocal leukoencephalopathy (PML), malignancies, serious infection, neurotoxicity	Pregnancy Category C
Retinoid					
Acitretin (Soriatane) 1996	Severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments	Starting dose: 25 to 50 mg orally (PO) per day, Maintenance doses of 25 to 50 mg per day may be given dependent upon an individual patient's response to initial Rx	From the label: 2 DB, PC trials- Mean change in PGA at 8 weeks A-Acitretin(50mg)-2 vs -0.29 on placebo B- Acitretin (50mg)-1.57 vs Acitretin (25 mg)-1.06 vs -0.06 on placebo (no multiplicity adjustment for trial B)	BW-pregnancy must be prevented during Rx and for 3 years following due to teratogenicity, no ethanol ingestion by females of childbearing potential (FOCBP) due to metabolism to etretinate and ↑ 1/2life, REMS (Do Your P.A.R.T.) participation required for FOCBP-see Drugs @ FDA for details.	W&P: hepatotoxicity, skeletal abnormalities, lipids↑, Cardiovascular risk ↑, Ophthalmologic effects, Pancreatitis, capillary leak syndrome, pseudotumor cerebri, exfoliative

Product (s) Name/year approved	Relevant Indication	Dosage & Admin	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				Patients cannot donate blood for 3 years post Rx, See label for data on pregnancies in partners of male patients on acitretin	dermatitis, depression Pregnancy category X
Phosphodiesterase 4 (PDE4) inhibitor					
Apremilast (Otezla) 2014	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	To reduce risk of gastrointestinal symptoms, titrate to recommended dose of 30 mg PO twice daily	From the label: 2 R, DB, PC trials PASI75 at 16 weeks 1- aprem[18]33% vs 5% in placebo 2- aprem 28.8% vs 5.8% in placebo	W&P: depression, weight decrease, drug interactions with strong P450 enzyme inducers (rifampin, phenobarbital, carbamazepine phenytoin)	Diarrhea, nausea, URI, headache Pregnancy Category C
Phototherapy					
PUVA-8-MOP (methoxsalen) + UVA therapy	Severe, recalcitrant, disabling psoriasis not responsive to other forms of therapy	20 -70 mg PO (based on weight) taken 2-4 hours before exposure to UVA light	No efficacy information for psoriasis in the label.	BW: Should only be used by MDs who have special competence in psoriasis management Warnings: serious skin burning, ocular damage, aging of the skin, skin cancer (including melanoma)	Nausea, erythema, pruritus, must avoid all exposure to sunlight (even through windows) to eyes and skin for 24 hours after ingestion; Pregnancy category C

[18] aprem=apremilast

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

CIMZIA (certolizumab pegol) is currently licensed in the United States for the following indications:

- 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
- Treatment of adults with moderately to severely active rheumatoid arthritis
- Treatment of adult patients with active psoriatic arthritis
- Treatment of adults with active ankylosing spondylitis

3.2. Summary of Presubmission/Submission Regulatory Activity

The applicant developed certolizumab injection under IND 100348, which was submitted on September 9, 2014. During the development program for plaque psoriasis, the applicant interacted with the Agency at the following milestone meetings (PIND 1/17/2007, End-of-Phase 6/11/2014, and Guidance meetings written responses dated 5/24/2016).

During the Pre-BB IND Meeting on January 17, 2007, the Agency recommended:

- Further Phase 2 dose ranging studies in plaque psoriasis subjects and advised to perform exposure-response analyses in the psoriasis population.
- Submission of the full details of proposed Phase 3 trials for review prior to conducting the trials.

An End-of-Phase 2 (EOP2) Meeting was held on June 11, 2014. In the meeting package, the applicant submitted protocols for Phase 3 trials PS0002 (placebo-controlled) and PS0003 (placebo- and active-controlled, etanercept). The following advice was provided to the applicant:

- The Agency disagreed with the use of concomitant psoriasis treatments to all affected body areas.
- The Agency recommended continued evaluation of 200mg and 400mg dosing, and requested a discussion of the characteristics of subjects in the Phase 2 certolizumab 200mg group who did not meet both the primary endpoints given the striking difference in PASI 75 and PGA outcomes.
- The Agency provided comments regarding primary endpoints, PGA scale, time-point for primary assessment, randomization, center-to-center variability, number of centers, primary analysis method, primary analysis population, methods for handling missing data, and approach for controlling the Type I error rate for multiplicity. In addition, the Agency provided comments regarding the maintenance period of PS0002.

An IND application was submitted by the applicant on September 10, 2014. The submission contained a protocol for a Phase 3 trial (PS0005). PS0005 was not discussed during the EOP2 meeting; however, the applicant stated that the study designs for PS0002 and PS0005 are identical. A Study May Proceed letter was sent to the applicant on November 25, 2014. The applicant addressed most of the comments provided during the EOP2 meeting. In the letter, the Agency reiterated the recommendation from the EOP2 meeting that the applicant evaluate outcomes during maintenance based on both PASI and PGA (i.e., not just PASI). In addition, the Agency reiterated the recommendation regarding the investigation of the center-to-center variability.

An agreed-upon Pediatric Study Plan was submitted by the applicant on January 20, 2015. (b) (4) the applicant had agreements for initiating studies in pediatric subjects with (b) (4) polyarticular-course juvenile idiopathic arthritis, and active Crohn's disease.

The following advice was provided by written response Type C guidance on May 24, 2016:

- The Agency recommended the applicant submit data to establish a scientific bridge between US-license ENBREL and EU-approved etanercept if a superiority claim to US-licensed Enbrel will be sought for CIMZIA.
- The content and format of the proposed BLA submission was reviewed.

None of the trials in the development program for certolizumab were conducted under a Special Protocol Assessment.

No pre-sBLA meeting was held for this application, but the questions and responses of the written response Type C guidance meeting on May 24, 2016 were typical of pre-sBLA meetings.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No clinical site inspections of domestic or international sites were done as part of this efficacy supplement.

4.2. Product Quality

Novel excipients: None
Any impurity of concern: None

4.3. Clinical Microbiology

Not applicable to this efficacy supplement.

4.4. Devices and Companion Diagnostic Issues

Not applicable to this efficacy supplement.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The applicant of CIMZIA submitted a prior approval efficacy supplement for the approval to market certolizumab pegol for the treatment of adults with moderate to severe chronic plaque psoriasis who are eligible for systemic therapy or phototherapy. Nonclinical pharmacology/toxicology studies were submitted and reviewed under the original BLA. No safety issues were identified and additional nonclinical studies are not needed to support the new efficacy supplement.

5.2. Referenced NDAs, BLAs, DMFs

N/A

5.3. Pharmacology

N/A

5.4. ADME/PK

N/A

5.5. Toxicology

N/A

5.6. Label

The nonclinical sections of the previously approved label have not been changed and are acceptable as submitted. Section 8.1 of the label was already in accordance with the Pregnancy and Lactation Labeling Rule and no changes are recommended. The nonclinical sections of the previously approved label have not been changed and are acceptable as submitted. Section 8.1 of the label was already in accordance with the Pregnancy and Lactation Labeling Rule and no changes are recommended.

6 Clinical Pharmacology

6.1. Executive Summary

Cimzia® (certolizumab pegol, CZP) is a recombinant, humanized antibody Fab' fragment against human tumor necrosis factor alpha (TNFα), conjugated to polyethylene glycol (PEG). Under BLA 125160, Cimzia was approved for the treatment of adult patients with Crohn's disease (CD) on 22 April 2008, for the treatment of adult patients with rheumatoid arthritis (RA) on 13 May 2009, for the treatment of psoriatic arthritis on 27 September 2013, and for the treatment of ankylosing spondylitis on 17 October 2013.

The current efficacy supplement application is for the inclusion of a new indication for CZP - treatment of adult subjects with moderate to severe chronic plaque psoriasis. The proposed dosing regimen for the treatment of moderate to severe chronic psoriasis is 400 mg every other week. A dose of 400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week may be considered.

The sBLA contains efficacy and safety data from two Phase 2 studies (C87040 and C87044) and three Phase 3 studies (CIMPASI-1, CIMPASI-2 and CIMPACT).

The key review findings with specific recommendations/comments are summarized below.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The efficacy of CZP for the treatment of moderate to severe psoriasis is established in three Phase 3 trials (CIMPASI-1, CINPASI-2 and CIMPACT). Dose-response and PK-PD modeling for efficacy based on data from Phase 3 trials provide supportive evidence for effectiveness.
General dosing instructions	The proposed dosing regimen (400 mg every other week) is acceptable. The alternative dosing regimen of 400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week is acceptable for subjects with body weight < 90 kg.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dose individualization based on intrinsic or extrinsic factors is not recommended; however, the lower dose of 400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week is recommended for subjects with body weight < 90 kg.
Labeling	The review team has specific content and formatting change recommendations.
Immunogenicity	Antibodies to CZP were associated with up to 20-fold lower serum CZP concentrations and reduced efficacy. The immunogenicity assays are subject to interference by serum CZP. See PMR recommendations.

6.1.1. Recommendations

From a clinical pharmacology standpoint, this supplemental BLA is acceptable to support the approval of CIMZIA (certolizumab pegol, CZP) for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

6.1.2. Post-Marketing Requirements and Commitment(s)

Clinical Pharmacology review team agrees with OBP review team to recommend that the Applicant conduct the following two PMCs:

- PMC 3408-5: Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to certolizumab pegol, including procedures for the accurate detection of binding antibodies to certolizumab pegol in the presence of certolizumab pegol levels expected in the serum or plasma at the time of patient sampling. In addition, an assessment of the contribution of binding antibodies to PEG should also be evaluated.

- PMC 3408-6: Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to certolizumab pegol, including procedures for the accurate detection of neutralizing antibodies to certolizumab pegol in the presence of certolizumab pegol levels that are expected in the serum or plasma at the time of patient sampling.

Clinical Pharmacology review team recommends that the Applicant conduct the following PMR:

- PMR 3408-2: Utilize the validated immunogenicity assays developed under PMC 3408-5 and PMC 3408-6 to analyze the immunogenicity profile of certolizumab pegol using banked patients samples from Phase 3 trials CIMPASI-1, CIMPASI-2 and CIMPACT. Evaluate the impact of immunogenicity on pharmacokinetics, efficacy, and safety in subjects with psoriasis based on the immunogenicity data generated with the newly validated assays.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics of CZP in subjects with psoriasis

The pharmacokinetic properties of CZP in subjects with moderate to severe psoriasis were generally similar to the PK properties in subjects with Crohn's disease and rheumatoid arthritis. Geometric mean CZP concentrations in subjects receiving the CZP 200 mg Q2W and CZP 400 mg Q2W dosage regimens were 17.32 mcg/mL and 47.95 mcg/mL, respectively, at week 16; 15.84 mcg/mL and 46.88 mcg/mL, respectively, at week 48. Apparent volume of distribution (V/F) and systemic clearance (CL/F) in psoriasis

patients were 4.71 L and 0.338 L/day, respectively, estimated based on population PK analysis. Body weight and ADA status were identified as most significant factors affecting CL/F and V/F. CL/F values were higher in subjects with higher body weight and in subjects who developed ADAs.

Immunogenicity and its impact on PK and efficacy

In the Phase 3 studies, the incidences of antibodies against CZP were 19.2% (54 of 281 subjects) and 8.3% (22 of 265 subjects) over the 48-week treatment period in the CZP 200 mg Q2W and CZP 400 mg Q2W groups, respectively. Of the subjects who developed antibodies to certolizumab pegol, 45% (27/60) had antibodies that were classified as neutralizing. However, due to low drug tolerance levels of the ADA assay and NAb assay, immunogenicity incidences may be underestimated. See section 6.3.2 for additional details.

Antibody formation was associated with significantly lower CZP serum concentration. The geometric mean CZP concentrations in ADA positive subjects were 9- to 11-fold lower at Week 16 and 14- to 20-fold lower at Week 48 compared to ADA negative subjects.

Development of ADAs was associated with reduced efficacy. The PASI 75 response rates were approximately 2-fold lower in ADA positive subjects compared to ADA negative subjects. Similar trends were also observed for other efficacy endpoints including PGA scores and PASI 90.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The applicant has proposed a dosing regimen of 400 mg every other week (400 mg Q2W) administered by SC injection. The applicant has also proposed an alternative dosing regimen of 400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week. The proposed regimens are supported by efficacy data from the Phase 3 trials (CIMPASI-1, CIMPARI-2 and CIMPACT). We recommend that the alternative dosing regimen for 200 mg Q2W be considered for subjects with body weight less than 90 kg based on available PK/PD data. Refer to Section 7 of this review for additional efficacy findings supporting the recommended dosing regimen.

Therapeutic Individualization

Population PK analysis identified body weight as a significant covariate that impacted CZP exposure. Further, body weight appeared to exhibit an impact on CZP efficacy. In subjects ≥90 kg, 13% and 9% greater response rates for PGA and PASI 75 were observed with the 400 mg Q2W regimen compared to 200 mg Q2W. In subjects < 90 kg, only 4 % and 1 % greater response rates for PGA and PASI 75 were observed with the 400 mg Q2W regimen compared to 200 mg Q2W. Overall, the dose-response results

across body weight subgroups support a recommendation of 400 mg Q2W for the overall population and that 200 mg Q2W may be considered in patients with body weight <90 kg.

Therapeutic individualization based on other intrinsic or extrinsic factors is not necessary.

Outstanding Issues

There are no outstanding issues that would preclude the approval of the current efficacy supplement from clinical pharmacology's perspective.

Both the ADA and NAb assays used to measure antibodies to certolizumab pegol are subject to interference by serum certolizumab pegol, possibly resulting in an underestimation of the immunogenicity incidences of antibody formation. The drug interference issue of the ADA assays could confound the interpretation of the ADA incidences across treatment groups varying in CZP exposure. The potential underestimation of the immunogenicity incidences would also affect the reliability of the analysis results for the immunogenicity impact on PK, efficacy and safety.

See PMR recommendations in section 6.1.2 relating to the immunogenicity assessment issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A summary of the general pharmacology, pharmacokinetics and immunogenicity of CZP relating to the psoriasis indication is provided in the table below (Table 2).

Table 2: Summary of pharmacology, pharmacokinetics and immunogenicity of CZP relating to psoriasis indication

Pharmacology	
Mechanism of Action	Certolizumab pegol is a recombinant, humanized antibody Fab' fragment against human tumor necrosis factor alpha (TNFα), conjugated to polyethylene glycol (PEG). TNFα is a key pro-inflammatory cytokine with a role in inflammatory disorders including psoriasis. CZP binds to TNFα, inhibiting its role as a key mediator of inflammation.
General Information	
Bioanalysis	CZP concentrations in human serum were quantified using a validated electrochemoluminescence (ECL) assay on a Meso Scale Discovery® (MSD) platform. The ECL assay had improved sensitivity (LLOQ of 0.032 mcg/mL) compared to the enzyme-linked immunosorbent assay

	(ELISA) assay (LLOQ of 0.412 mcg/mL) used in previous clinical trials. Both assays have been validated for the quantification of CZP in human serum and the two assays have been demonstrated comparable. See Section 13.4 for additional details.
PK in psoriasis subjects	The PK properties of CZP in subjects with moderate to severe psoriasis were generally similar to the PK properties in subjects with Crohn's disease and rheumatoid arthritis. Apparent volume of distribution (V/F) and systemic clearance (CL/F) in psoriasis patients were 4.71 L and 0.338 L/day, respectively, estimated based on population PK analysis. Geometric mean CZP concentrations in subjects receiving the CZP 200 mg Q2W and CZP 400 mg Q2W dosage regimens were 17.32 mcg/mL and 47.95 mcg/mL, respectively, at week 16; 15.84 mcg/mL and 46.88 mcg/mL, respectively, at week 48.
Body weight	Population PK analysis identified body weight as a significant covariate affecting CZP exposure in subjects with psoriasis. CL/F values were higher in subjects with higher body weight. See Section 6.3.2 for additional details.
Immunogenicity	
Incidence	In the psoriasis Phase 3 studies, 54 of 281 (19.2%) subjects receiving the 200 mg Q2W regimen and 22 of 265 (8.3%) subjects receiving the 400 mg Q2W regimen were ADA positive during the 48-week treatment period. The incidence of ADAs was lower at 400 Q2W compared to 200 Q2W; however, the comparison of ADA incidences is confounded by the low drug tolerance of the ADA assay which could result in an underestimation of the ADA incidence at higher drug concentrations. Of the 60 subjects in the Phase 3 studies who were anti-body positive, only 27 subjects were evaluable for neutralizing antibodies and all of them tested positive for neutralizing antibodies.
Impact on PK	Immunogenicity has a negative impact on systemic exposure of CZP. The development of ADA is associated with reduced plasma CZP concentrations. In the Phase 3 studies, the geometric mean CZP concentrations were lower in ADA positive subjects than those in the corresponding ADA negative subjects starting at Week 4 through Week 48.
Impact on efficacy	Occurrences of ADA generally lead to a detrimental effect on efficacy. The efficacy responses were generally lower in ADA positive subjects compared to ADA negative subjects. PGA and PASI75 responder rates were lower (at least 2-fold) at Week 48 in ADA positive subjects compared with ADA negative subjects in both the CZP 200 mg Q2W and CZP 400 mg Q2W groups. Similar trends were observed at Week 16.

6.3.2. Clinical Pharmacology Questions

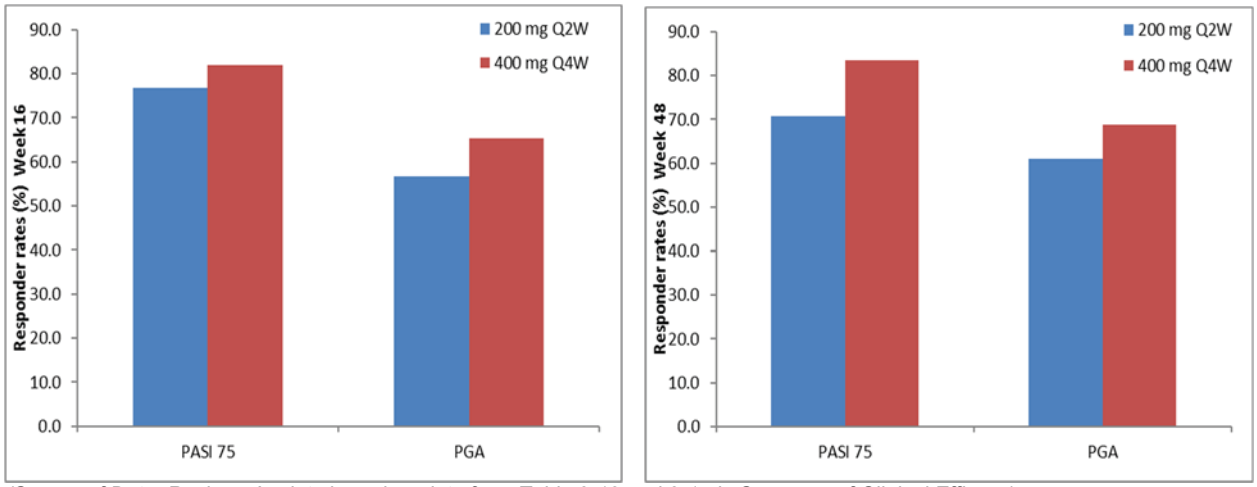
Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The overall Phase 3 efficacy results provide evidence that CZP is effective for the treatment of adult patients with moderate to severe psoriasis. The dose-response and exposure-response relationships for PGA and PASI 75 have provided supportive evidence of effectiveness.

Dose-response for efficacy in Phase 3 trials

A dose-response relationship for efficacy was observed for PGA and PASI 75 at both Week 16 and Week 48 with numerically greater response rates observed for the CZP 400 mg Q2W dosing regimen compared to the CZP 200 mg Q2W dosing regimen (Figure 1). The co-primary efficacy endpoints are PASI 75 and PGA responder rates at Week 16. Efficacy data from all three individual studies as well as pooled analysis results have demonstrated that both 200 mg Q2W and CZP 400 mg Q2W dosing regimens were efficacious at Week 16 compared to placebo. See Section 7 of this multi-discipline review for evaluation and details of the study design and results of the Phase 3 studies.

Figure 1: PASI 75 and PGA responder rates at Week 16 and Week 48 in subjects treated with CZP 200 mg Q2W and CZP 400 mg Q2W based on pooled analysis in the Phase 3 studies



(Source of Data: Reviewer's plots based on data from Table 3-12 and 3-14 in Summary of Clinical Efficacy)

Exposure-response for efficacy

An exposure-response relationship was observed for efficacy variables including PASI 75 and PGA in a population PK/PD model-based analysis conducted by the Applicant using data from psoriasis Phase 3 studies. Figure 2 shows the model predicted PASI score versus CZP steady state trough concentrations at Week 16 co-plotted with the observed CZP trough concentrations and PASI score in Phase 3 trials.

Figure 2: Model-predicted and observed PASI scores versus predicted CZP plasma concentration at Week 16 in CIMPASI-1, CIMPASI-2, and CIMPACT

The population PK/PD model was established using an indirect response model in which CZP inhibits the production of the response. The CZP-induced effect was included as a sigmoid Emax model using the individual predicted CZP plasma concentrations as predictors of the response. See Clinical Pharmacology Appendix for more details. The clinical pharmacology review team has verified the PK-PD model developed by the Applicant. *(Source of data: Figure 33, Applicant's population PK and PK-PD report)*

The population PK/PD analysis results in general support a greater reduction of PASI score being associated with increasing CZP concentrations. The PK/PD model also shows that the two CZP dose levels (200 mg Q2W and 400 mg Q2W) have overlap of CZP concentrations and the clinical response for PASI has reached plateau in the exposure-response curve suggesting that higher doses are not likely to improve efficacy.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Dose adjustment based on body weight is not necessary for the recommended dose of 400 mg Q2W based on the available PK and efficacy data in Phase 3 trials. However, for subjects with body weight <90 kg, the dosing regimen of 200 mg Q2W can be considered.

Effect of body weight on PK

Lower CZP plasma concentrations were observed in subjects with higher body weight. The population PK analysis identified body weight as one significant covariate that influences PK of CZP in psoriasis subjects. CZP CL/F and V/F increase with increasing body weight. Population PK model-predicted CZP trough concentrations by body weight quintiles are shown in Table 3.

Table 3: Predicted CZP trough concentrations at Week 16 by body weight quantile

Dose	Stratification (kg)	CZP C_{trough} concentrations (µg/mL)	
		Median	5th to 95th percentiles
CZP 200mg Q2W	41.8 to 74.5	34.83	18.7 to 59.2
	74.5 to 84.5	27.30	7.70 to 44.6
	84.5 to 94.3	24.60	6.96 to 40.1
	94.3 to 107.5	21.11	3.52 to 35.1
	107.5 to 198.5	16.51	2.35 to 28.9
CZP 400mg Q2W	41.8 to 74.5	69.08	37.4 to 115
	74.5 to 84.5	54.37	15.1 to 87.1
	84.5 to 94.3	48.93	13.7 to 78.8
	94.3 to 107.5	42.18	6.97 to 69.0
	105.5 to 198.5	32.92	4.68 to 57.1

CZP=certolizumab pegol; PK-PD=pharmacokinetic-pharmacodynamic; Q2W=every 2 weeks
(Source of data: Table 3-3 from Summary of Clinical Pharmacology)

Effect of body weight on efficacy:

Body weight had an effect on efficacy of CZP in psoriasis clinical trials. Table 4 illustrates responder rates at Week 16 and Week 48 by body weight subgroups and by 200 mg Q2W and 400 mg Q2W dosing regimens in Phase 3 trials. The Applicant also conducted population PK/PD analysis that evaluated the body weight effect on efficacy. The results show the following:

- Subjects with higher body weight were associated with lower clinical response rates at the same dosing regimen. At 200 mg Q2W, subjects ≥90 kg had 18-22 % and 14-24 % lower response rates at Week 16 and Week 48, respectively, compared to subjects <90 kg. At 400 mg Q2W, subjects ≥90 kg had 10-21 % and 9- 24 % lower response rates at Week 16 and Week 48, respectively, compared to subjects <90 kg.
- Dose-response relationships were observed in both subjects <90 kg and subjects ≥90 kg, supporting 400 mg Q2W as the recommended dosing regimen for all subjects regardless of body weight.
- In subjects ≥90 kg, the clinical response rate differences between the two dosing regimens were 4-13% at Week 16 and 2-11% at Week 48 across the efficacy endpoints. In subjects <90 kg, a smaller clinical response rate differences were observed between the two dosing regimens with 1-4% at Week 16 and 3-8% at Week 48 across the efficacy endpoints. The differential dose-response by body weight groups would support that the dosing regimen of 200 mg Q2W may be preferentially considered for subjects <90 kg.
- The population PK-PD analysis indicated that body weight affects PASI t1/2 the parameter reflecting the time to maximum response. PASI t1/2 appears to be longer as body weight increases, indicating that it takes longer to achieve steady state clinical response in heavier subjects (for example, 16 weeks for a 90kg subject versus 21 weeks for a 150kg subject). However, these results indicate that with ADA status adjusted, a higher dose of 400 mg Q2W provides only a marginal

improvement in higher body weight subjects compared to 200 mg Q2W at both week 16 as well as week 48. See Clinical Pharmacology appendix for more information.

Table 4: Effect of body weight on pooled response rates in low and high body weight subgroups for subjects dosed with 200 Q2W and 400 mg Q2W in the Phase 3 studies.

Efficacy variable: Responder rates (%)	Week 16				Week 48			
	BW <90kg		BW ≥90kg		BW <90kg		BW ≥90kg	
	200 mg Q2W	400 mg Q2W	200 mg Q2W	400 mg Q2W	200 mg Q2W	400 mg Q2W	200 mg Q2W	400 mg Q2W
	N=175	N=206	N=176	N=136	N=175	N=206	N=176	N=136
PGA	65.0	69.4	42.9	56.0	66.3	69.1	42.5	44.9
PASI75	81.0	81.9	63.5	72.3	71.3	77.3	56.6	67.9
PASI90	50.9	56.7	32.1	36.2	53.8	61.9	39.6	47.4

(Source of data: RFI dated 25th January 2018)

Safety considerations
There were no clear differences in the safety profile of CZP across low body weight and high body weight subjects within the same dosing regimen (200 mg Q2W or 400 mg Q2W) at the primary endpoint at Week 16. However, in considering the data from the entire treatment period covering the initial, maintenance and OLE treatment phases the incidences of any TEAE were slightly higher in the CZP 400 mg Q2W group compared with the CZP 200 mg Q2W group regardless of weight category, which would support the inclusion of the 200 mg dose as an alternative recommended dosing regimen for some patients. See section 7 of the multidisciplinary review for additional safety information.

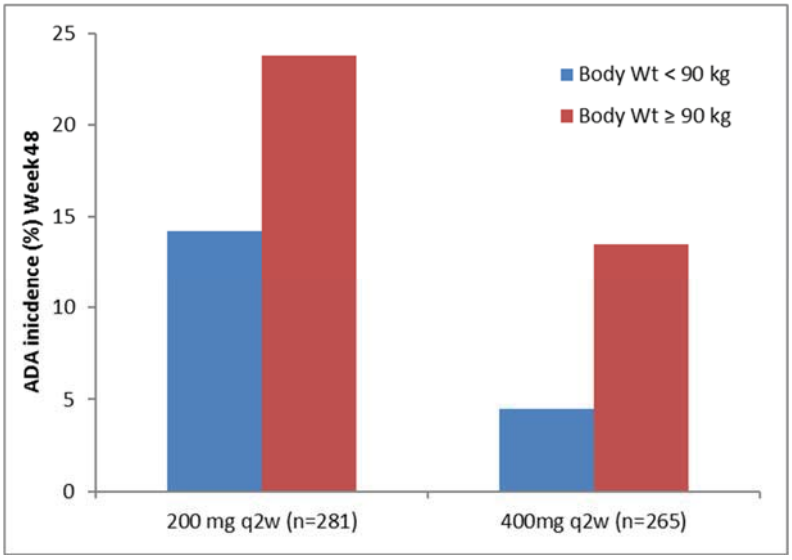
What is the overall incidence of immunogenicity to CZP? What is the impact of immunogenicity on PK and efficacy?

Immunogenicity incidences for ADA
Among the evaluated subjects, 54 of 281 (19.2%) subjects who were on the 200 mg Q2W regimen were ADA positive compared with 22 of 265 subjects (8.3%) who were on the 400 mg Q2W regimen over the 48-week study period across the three Phase 3 studies (Table 5). It is observed that subjects <90 kg were associated with lower ADA incidences compared to subjects ≥90 kg (Figure 3). Although the underlying mechanism is not clear, the observation of the lower ADA incidence at 400 Q2W (compared to 200 Q2W) and lower ADA incidence in subjects <90 kg (compared to subjects ≥90 kg) could be confounded by the known low drug tolerance of the ADA assay which can lead to underestimation of the ADA incidence when CZP levels in plasma are higher than the tolerance limit for the assay.

Table 5: Incidence of ADAs against CZP over a 48 week treatment period in subjects with psoriasis treated with CZP 200 mg Q2W or CZP 400 mg Q2W.

	CZP 200 mg Q2W n/Nobs (%)	CZP 400 mg Q2W n/Nobs (%)
ADA negative	227/281 (80.8)	243/265 (91.7)
ADA positive	54/281 (19.2)	22/265 (8.3)

Figure 3: Incidence of anti-drug antibodies during the initial and maintenance treatment periods stratified by dose and by body weight category



(*Source of data: Reviewer generated plot based on Applicants response to RFI dated 25th Jan 2018*)

Time-course of ADA formation

Summary of first occurrence of ADA incidence over the 48-week treatment period is provided in Table 6. It is noted that majority of the subjects for both dose groups who tested ADA positive had their first occurrence of a positive result at Week 16 (i.e., they became ADA positive at some point after Week 4 and were determined to be ADA positive at Week 16). The time-course of ADA formation was consistent with the PK profile observed in the ADA positive subjects (see sections below).

Table 6: First occurrence of positive anti-CZP antibody status by visit across the Phase 3 studies

	CZP 200 mg Q2W n/Nobs (%) [cc]	CZP 400 mg Q2W n/Nobs (%) [cc]
Baseline	0/282	0/267 [0]
Week 2	0/277	1/261 (0.4) [1]
Week 4	1/275 (0.4) [1]	1/260 (0.4) [2]
Week 16	43/273 (15.8) [44]	13/256 (5.1) [15]
Week 24	1/253 (0.4) [45]	6/241 (2.5) [21]
Week 32/36	6/241 (2.5) [51]	0/230 [21]
Week 48 (OLE Week 0)	3/228 (1.3) [54]	1/223 (0.4) [22]
Follow-up (Week 10)	5/32 (15.6) [59]	4/21 (19.0) [26]

cc=cumulative count; Nobs=numbers observed;

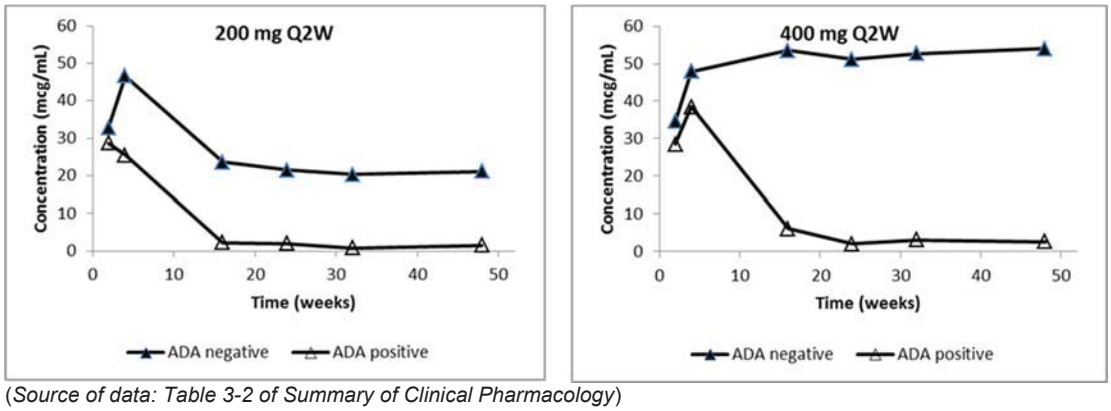
Immunogenicity incidences for neutralizing ADA

Of the 60 subjects in the Phase 3 studies CIMPASI-1 and CIMPASI-2 who were anti-body positive, only 27 subjects were evaluable for neutralizing antibodies. This was due to the low drug tolerance of the neutralizing antibody assay (< 0.3mcg/mL). All the 27 ADA positive subjects who were tested for neutralizing antibody tested positive for neutralizing antibodies. Considering the limitation of the neutralizing antibody assay in the presence of CZP, the number of subjects with neutralizing antibody in these studies may be significantly underestimated.

Immunogenicity impact on PK

The development of ADA is associated with a decrease in mean plasma CZP concentrations (Figure 4). Across the three Phase 3 studies, the geometric mean CZP concentrations were lower in ADA positive subjects than those in the corresponding ADA negative subjects. CZP concentrations were notably lower at later time points up to Week 48 among ADA positive subjects compared with ADA negative subjects.

Figure 4: Effect of ADA status on CZP serum concentrations in the Phase 3 studies at the 200 Q2W and 400 mg Q2W dosing regimens.



(*Source of data: Table 3-2 of Summary of Clinical Pharmacology*)

Reviewer's comment*: The observed PK data in ADA positive subjects with close-to-zero drug concentrations indicated that the estimated immunogenicity impact of 3-fold increase in clearance based on population PK analysis could be an underestimation.*

Immunogenicity impact on efficacy
Occurrences of ADA against CZP generally lead to a detrimental effect on efficacy. The efficacy responses were generally lower in ADA positive subjects compared to ADA negative subjects (Table 7). PGA and PASI 75 responder rates were lower (at least 2-fold) at Week 48 in ADA positive subjects compared with ADA negative subjects in both the CZP 200 mg Q2W and CZP 400 mg Q2W groups. Similar trends were observed at Week 16.

Table 7: Effect of ADA status on PGA and PASI75 responder rates at Week 48 in subjects pooled across the various Phase 3 studies dosed with CZP at 200 mg Q2W or 400 Q2W.

CZP Dosing regimen	Endpoint	Responder rates at Week 48 (%)	
		ADA negative	ADA positive
200 mg Q2W	PGA	90/152 (59.2)	8/34 (23.5)
	PASI 75	107/152 (70.4)	10/34 (29.4)
400 mg Q2W	PGA	101/158 (63.9)	1/17 (5.9)
	PASI 75	123/158 (77.8)	5/17 (29.4)

(*Source of data: Table 3-37 of Summary of Clinical Efficacy*)

Summary of immunogenicity assays
Presence of anti-drug (CZP) antibodies (ADAs) in human serum was assessed using a validated screening ELISA method based on a double-antigen sandwich (bridge) based immunoassay (Method Validation Report 40001529). This ELISA assay used for ADA detection in the psoriasis studies is the same as that used in the original BLA application. The assay has a known drug interference issue, i.e., ADA is detectable only when serum CZP levels are <0.5 mcg/mL which is lower than the observed concentrations of CZP observed in psoriasis subjects in these studies (Table 8).

The neutralizing activity of ADAs was evaluated using a validated HeLa cell bioassay (Method Validation Report AR6633). Analogous to the ADA assay, this assay also has a low drug tolerance i.e. NAb can be detected reliably only when serum CZP levels are <0.3 mcg/mL. Therefore, it is only feasible to characterize NAb status for a subset of immunogenicity samples.

Refer to the OBP review in the current submission and original BLA review for additional details about the immunogenicity assays.

Table 8: Sensitivity and drug tolerance of the immunogenicity assays for detecting binding (ADA) and neutralizing anti-drug antibodies (NAb) against CZP in Phase 3 psoriasis studies.

Immunogenicity Assays	Sensitivity	Drug tolerance	CZP concentration at Week 48 (Geo. Mean)	
			200 mg Q2W	400 mg Q2W
ADA Assay	63 ng/mL	0.5 mcg/mL of CZP (using 10 mcg/mL of control); 2 mcg/mL of CZP (using 20 mcg/mL of control)	15.84 mcg/mL	46.88 mcg/mL
NAb assay	156 ng/mL	0.02 mcg/mL of CZP (using 15 mcg/mL of control) 1.14 mcg/mL of CZP (using 100 mcg/mL of control)		

(*Source of Data: Summary of Biopharmaceutic Studies and Associated Analytical Methods; Applicant's method validation reports, 40001529 and AR6633*)

Reviewer's comments*: The current product labeling has a general statement suggesting that the assay used for immunogenicity assessment can have an impact on reported immunogenicity data. We have proposed modifying the labeling language to specifically indicate that the immunogenicity incidences may be underestimated because of the low drug tolerance of the ADA assay. We agree with the OBP review team to recommend PMCs for the Applicant to address the drug interference issue of the ADA assay and the NAb assay. See Section 6.1.2.*

7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

The development program for certolizumab included five clinical trials. The applicant completed two Phase 2 trials (C87040 and C87044) and three Phase 3 trials (PS0005, PS0002, and PS0003). The primary data used to support the safety and efficacy of certolizumab for the treatment of moderate to severe plaque psoriasis in adults was provided by these Phase 2 and 3 studies. In addition, long-term safety was supported by integrated data from the ongoing Phase 3 extension trials (PS0005, PS0002, and PS0003) with a cutoff date of June 30, 2017 (Safety Update cut date). The data associated with different doses, dosing regimens, routes of administration, and study populations were considered supportive of the conclusions of the primary analyses.

Table 9: Listing of Clinical Trials Relevant to BLA 125160

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
PS0005 (CIMPASI 1)	Phase 3, 144-Week, multicenter, randomized, double- blind, placebo - controlled trial to assess safety and efficacy followed by a maintenance period and long term safety extension	Initial[19] Placebo SC Q2W Cert[20] 400mg SC Q2W Cert 200mg SC: 400mg Week 0, 2, and 4 followed by 200mg Q2W Maintenance Placebo SC Q2W Cert400mg SC Q2W Cert 200mg SC: 400mg Week 0, 2, and 4 followed by 200mg Q2W Open-label Cert 400mg SC Q2W Cert 200mg SC: 400mg Week 0, 2, and 4 followed by 200mg Q2W	Co-primary efficacy proportion of subjects who achieved PASI 75 response at Week 16 and proportion of subjects with a PGA score of 0 “clear”) or 1 (“almost clear”), with at least a 2-grade reduction from baseline, at Week 16	Initial: Week 0-16 Maintenance: Week 16-48 Open-label: Week 48-144	Randomized: 227 Placebo: 49 Cert 400mg: 87 Cert 200mg: 92	Men and women age 18 years and older with moderate to severe plaque-type psoriasis for at least 6 months who were candidates for phototherapy or systemic therapy. Moderate to severe psoriasis defined as PASI score ≥12, PGA score ≥3 and BSA ≥10%.	30 sites USA: 78 subj[21] Canada: 42 subj Czech Rep: 24 subj Germany: 76 subj Hungary: 13 subj
PS0002 (CIMPASI 2)	Identical to PS0005	Identical to PS0005	Identical to PS0005	Identical to PS0005	Randomized: 234 Placebo: 51 Cert 400mg: 88 Cert 200mg: 95	Identical to PS0005	23 sites USA: 97 subj Austria: 7 subj Canada: 60 subj Poland: 63 subj

[19] Initial and Maintenace Peirod injections done by site staff. Open-label: subjects self-administered study medication.
[20] cert=certolizumab
[21] subj=subjects

PS0003 (CIMPACT)	Phase 3, 144-Week, multicenter, randomized, double- blind, placebo – controlled, active comparator-controlled trial to assess safety and efficacy followed by a maintenance period and long term safety extension	Initial Placebo[22] SC Q2W Cert 400mg SC Q2W Cert 200mg SC: 400mg Week 0, 2, and 4 followed by 200mg Q2W Etn[23] 50mg SC BIW Maintenance Placebo SC Q2W Cert 400mg SC Q2W Cert 400mg SC Q4W Cert 200mg SC: 400mg Week 0, 2, and 4 followed by 200mg Q2W Open-label Cert400mg SC Q2W Cert 200mg SC: 400mg Week 0, 2, and 4 followed by 200mg Q2W	Primary efficacy proportion of subjects who achieved PASI 75 response at Week 12 Key Secondary efficacy and the proportion of subjects with a PGA score of 0 (“clear”) or 1 (“almost clear”), with at least a 2-grade reduction from baseline, at Week 12 and Week 16, PASI at Week 16	Initial: Week 0-16 Maintenance: Week 16-48 Open-label: Week 48-144	Randomized: 559 Placebo: 57 Cert 400mg: 67 Cert 200mg: 65 Etn 50mg: 170	Men and women age 18 years and older with moderate to severe plaque-type psoriasis for at least 6 months who were candidates for phototherapy or systemic therapy. Moderate to severe psoriasis defined as PASI score ≥12, PGA score ≥3 and BSA ≥10%.	70 sites USA: 63 subj Bulgaria: 18 subj Czech Rep: 56 subj France: 9 subj Germany: 46 subj Hungary: 15 subj Netherlands: 3 subj Poland: 163 subj UK:16 subj
Studies to Support Safety							
C87040	Phase 2, 12-Week, multicenter, dose-response, randomized, double-bind, placebo-controlled trial to assess safety and efficacy	Placebo SC Q2W Cert 400mg SC Q2W Cert 200mg SC: 400mg Week 0 followed by 200mg Q2W	Primary efficacy proportion of subjects who achieved PASI 75 response at Week 12	Treatment: Week 0-12 Follow-up: Week 12-26	Randomized: 176 Placebo: 59 Cert 400mg: 58 Cert 200mg: 59	Men and women age 18 years and older with moderate to severe plaque-type psoriasis for at least 6 months who	France: 5 sites Germany: 10 sites

[22] Blinded certolizumab and placebo treatments administered during Week 0-16. Etanercept administered by unblinded staff or self-administered.
[23] etn=etanercept

	at 2 dosing regimens		and proportion of subjects with a PGA score of 0 “clear”) or 1 (“almost clear”), with at least a 2-grade reduction from baseline, at Week 12			were candidates for phototherapy or systemic therapy. Moderate to severe psoriasis defined as PASI score ≥12 and BSA ≥10%.	
C87044	Follow-up study of Trial C87040	Cert 400mg SC Q2W Cert 200mg SC Q2W	primary efficacy the difference in PASI scores between Week 12 score of the C87040 study and Week 12 score of re-treatment Study C87044	Treatment: Week 0-12 Follow-up: Week 12-26	73 subjects from C87040 Cert 400mg: 37 Cert 200mg: 34	Subjects from C87040 who responded (PASI75) at Week 12 and subsequently relapsed (>50% reduction in maximum improvement in PASI from baseline) during Week 12-36 of C87040	France: 4 sites Germany: 8 sites

7.1.2. Review Strategy

Data Sources

The sources of data used for the evaluation of the efficacy and safety of certolizumab for the proposed indication included final study reports submitted by the applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] and literature references.

This application was submitted in eCTD format and entirely electronic. The electronic submission including protocols, statistical analysis plans (SAPs), clinical study reports, SAS transport datasets in legacy, Study Data Tabulation Modal (SDTM), and Analysis Data Model (ADaM) format are located in the following network path:

Original submission: \\CDSESUB1\evsprod\BLA125160\0491\

Data and Analysis Quality

In general, the data submitted by the applicant to support the efficacy and safety of certolizumab for the proposed indication appeared adequate. A final statistical analysis plan (SAP) was submitted and most relevant analysis decisions (e.g., pooling of sites, analysis population membership, etc.) were made prior to unblinding.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Study Design and Endpoints

The applicant conducted three Phase 3 trials (Trials PS0002, PS0003, and PS0005). For all three trials, the key inclusion criteria that defined the study population were identical and are as follows:

- Male or female 18 years of age or older
- Chronic plaque psoriasis for at least 6 months
- Candidate for systemic therapy and/or phototherapy and/or chemophototherapy
- Have moderate to severe plaque psoriasis at baseline defined as:
  - Physician's Global Assessment (PGA) score ≥ 3, see Table 34 in Section 13.3
  - Psoriasis Area and Severity Index (PASI) score ≥ 12, see Figure 19 in Section 13.3 for details on the calculation of PASI
  - Body Surface Area (BSA) involvement ≥ 10%

Trials PS0002 and PS0005 were identically designed, and Figure 5 presents the study design schematic for these trials. Figure 2 presents the study design schematic for Trial PS0003. All three were multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 trials evaluating the safety and efficacy of Cimzia for the treatment of moderate to severe plaque psoriasis. All three trials evaluated two dose regimens of Cimzia (400 mg loading doses at Weeks 0, 2, and 4 followed by 400 mg every 2 weeks [Q2W] or 200 mg Q2W) during a 16-week initial treatment period (Week 0 through Week 16). Trial PS0003 also included an active comparator (etanercept).

For Trials PS0002 and PS0005, the protocols specified randomizing approximately 225 subjects in a 2:2:1 ratio (Cimzia 400 mg Q2W, Cimzia 200 mg Q2W, and placebo) and stratifying the randomization by investigational site. Subjects who did not achieve PASI 50 (i.e., ≥50% reduction from baseline in PASI) at Week 16 were escaped from blinded treatment and received open-label Cimzia 400 mg Q2W. If a subject who transitioned to the escape arm did not achieve a PASI 50 after 16 weeks of treatment in the escape arm, he/she was withdrawn from the trial. Subjects who achieved a PASI 50 response at Week 16 continued blinded therapy as follows:

- Subjects randomized to Cimzia 200 mg Q2W continued Cimzia 200 mg Q2W
- Subjects randomized to Cimzia 400 mg Q2W continued Cimzia 400 mg Q2W
- Subjects randomized to placebo who achieved a PASI 75 (i.e., ≥75% reduction from baseline in PASI) at Week 16 continued placebo
- Subjects randomized to placebo who did not achieve a PASI 75 at Week 16 received Cimzia 200 mg Q2W (following a loading dose of Cimzia 400 mg at Weeks 16, 18, and 20)
- From Week 32 through Week 48, all subjects who did not maintain PASI 50 were withdrawn from the trial

All subjects in Trials PS0002 and PS0005 who completed the Week 48 visit and maintained PASI 50 entered an open-label extension treatment period (Weeks 48 to

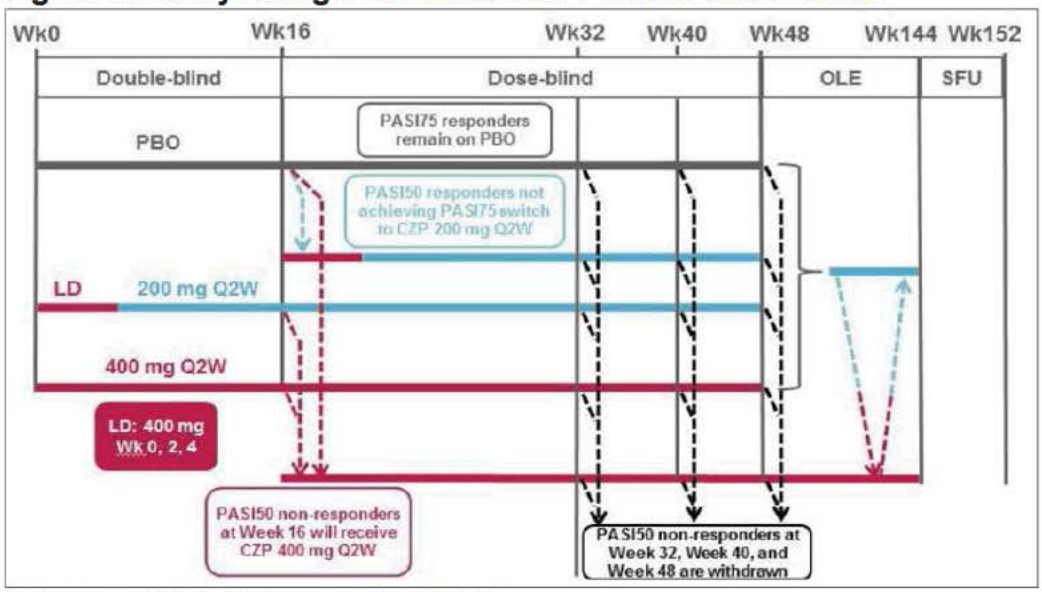
144) during which they received Cimzia 200 mg Q2W. Those subjects in the escape arm who completed the Week 48 visit entered the open-label treatment period and continued to receive Cimzia 400 mg Q2W.

For Trial PS0003, the protocol specified randomizing approximately 540 subjects in a 3:3:3:1 ratio (Cimzia 400 mg Q2W, Cimzia 200 mg Q2W, etanercept, and placebo) and stratifying the randomization by investigational site. Subjects who did not achieve a PASI 75 at Week 16 escaped from blinded treatment and received open-label Cimzia 400 mg Q2W. If a subject who transitioned to the escape arm did not achieve a PASI 50 after 16 weeks of treatment in the escape arm, he/she was withdrawn from the trial. Subjects who did achieve PASI 75 at Week 16 continued blinded therapy as follows:

- Subjects randomized to placebo continued to receive placebo
- Subjects randomized to etanercept were re-randomized in a 2:1 ratio to receive either Cimzia (loading dose of 400 mg at Weeks 16, 18, and 20 followed by 200 mg Q2W) or placebo
- Subjects initially randomized to Cimzia 200 mg Q2W were re-randomized in a 2:2:1 ratio to receive either Cimzia 200 mg Q2W, Cimzia 400 mg Q4W or placebo
- Subjects initially randomized to Cimzia 400 mg Q2W were re-randomized in a 2:2:1 ratio to receive either Cimzia 200 mg Q2W, Cimzia 400 mg Q2W or placebo
- From Week 32 through Week 48, all subjects who did not maintain PASI 50 entered the open-label extension period and received Cimzia 400 mg Q2W

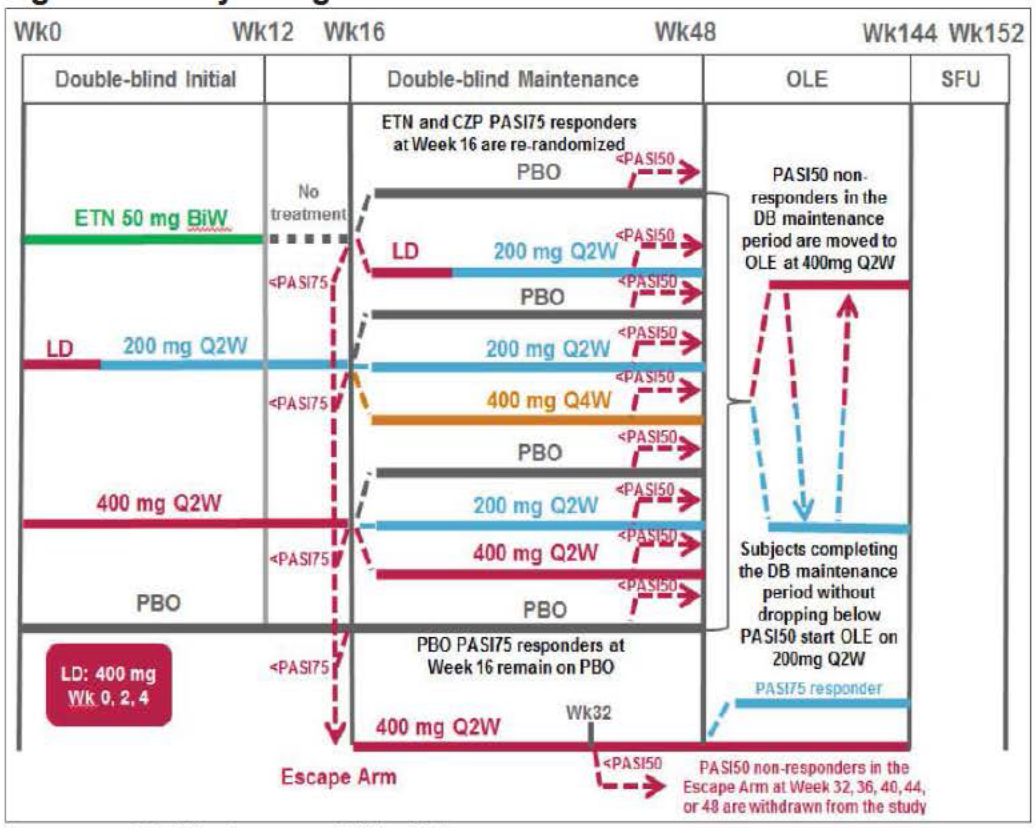
All subjects in Trial PS0003 who completed the Week 48 visit and maintained PASI 50 entered the open-label extension treatment period (Weeks 48 to 144) during which they received Cimzia 200 mg Q2W.

Figure 5: Study Design Schematic for PS0002 and PS0005



Source: page 17 of the Summary of Clinical Efficacy
CZP=certolizumab pegol; LD=loading dose; OLE=open-label extension; PASI 50=at least 50% reduction from baseline in PASI; PASI 75=at least 75% reduction from baseline in PASI; PBO=placebo; Q2W=every 2 weeks; SFU=Safety Follow-Up; Wk=week

Figure 6: Study Design Schematic for Trial PS0003



Source: page 20 of the Summary of Clinical Efficacy
BiW=twice weekly; CZP=certolizumab pegol; DB=double-blind; ETN=etanercept; LD=loading dose; PASI 50=at least 50% reduction from baseline in PASI; PASI 75=at least 75% reduction from baseline in PASI; PBO=placebo; OLE=Open-Label Extension; Q2W=every 2 weeks; Q4W=every 4 weeks; SFU=Safety Follow-Up; Wk=week

For Trials PS0002 and PS0005, the protocol-specified co-primary efficacy endpoints were:

- Proportion of subjects achieving a PGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline at Week 16
- Proportion of subjects achieving PASI 75 at Week 16

The protocols for Trials PS0002 and PS0005 specified the following as secondary efficacy endpoints:

- Proportion of subjects achieving PASI 90 at Week 16
- Proportion of subjects achieving a PGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline at Week 48
- Proportion of subjects achieving PASI 75 at Week 48
- Change from baseline in DLQI at Week 16

For Trial PS0003, the protocol-specified primary efficacy endpoint was the proportion of subjects achieving PASI 75 at Week 12. The protocol for Trial PS0003 specified the following secondary efficacy endpoints:

- Proportion of subjects achieving a PGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline at Week 12
- Proportion of subjects achieving PASI 90 at Week 12
- Proportion of subjects achieving PASI 75 at Week 16
- Proportion of subjects achieving a PGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline at Week 16
- Proportion of subjects achieving PASI 90 at Week 16
- Proportion of subjects achieving a PGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline at Week 48

For all three trials, the protocols specified many "other" secondary efficacy endpoints; however, these endpoints were not included in the multiplicity testing strategy. Therefore, the results of these endpoints are considered exploratory and are not included in this review. Section 7.2.2 provides details on how the primary and secondary efficacy endpoints listed above were analyzed across the various treatment arms.

Refer to Section 13.3 for the scales used to evaluate efficacy.

7.2.2. Statistical Methods

Refer to Section 3.2 for the regulatory history regarding the protocols and statistical analysis plan.

The protocol-specified primary analysis population was the Randomized Set (RS), defined as all randomized subjects. The protocol also specified conducting analyses using the Per-Protocol Set (PPS), defined as all subjects in the RS who have completed a minimal exposure of 16 weeks to the treatment regimen without any important protocol deviations that may "influence the validity of the data for the co-primary efficacy variables." The PPS excluded subjects who met any of the following criteria:

- Have taken any prohibited concomitant medications
- Did not attend the Week 16 visit
- Have not been compliant with the dosing regimen
- Out of visit window at the Week 16 visit

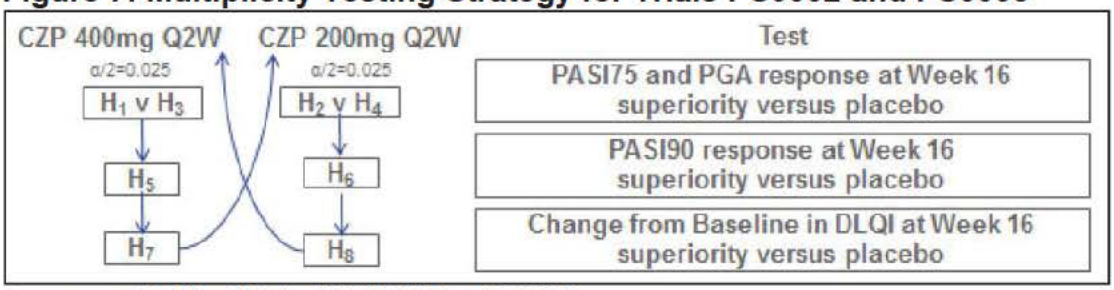
The statistical analysis plans (SAPs) for Trials PS0002 and PS0005 specified pooling centers that had less than 20 subjects. For Trial PS0003, the SAP specified pooling centers that had less than 30 subjects. Within each geographic region, the SPAs specified that centers with less than the specified minimum were to be ordered from largest to smallest and combined until the minimum number of subjects is reached. The SAPs specified that if 70% or more of the subjects came from centers that had less than

the specified minimum (i.e., 20 for Trials PS0002 and PS0005 and 30 for Trial PS0003), then pooling with be done based on geographic region.

The protocol-specified analysis method for binary efficacy endpoints was logistic regression with treatment group, pooled center (or geographic region), and prior biologic exposure (yes/no) in the model. For the analysis of change in DLQI from baseline to Week 16 (i.e., a secondary efficacy endpoint in Trials PS0002 and PS0005), the protocol-specified analysis method was analysis of covariance (ANCOVA) with treatment group, pooled center (or geographic region), and prior biologics exposure (yes/no) as factors and baseline DLQI score as a covariate.

For Trials PS0002 and PS0005, the protocols specified that the analysis for each dose will be carried out in separation of one another and the alpha level for the two dose comparisons will be 0.025 instead of 0.05 to control the Type I error rate for testing the two Cimzia doses (200 mg and 400 mg) against placebo. In addition, the protocols specified using a sequential gatekeeping approach to control the Type I error rate for testing two secondary endpoints (i.e., PASI 90 at Week 16 and change from baseline in DLQI at Week 16). The SAPs for Trials PS0002 and PS0005 specified a slightly different approach to control Type I error rate, see Figure 7. If all hypotheses within one set of hypotheses for a particular dose of Cimzia have been rejected at the 2-sided alpha level of 0.025, then the SAPs allowed for the alpha for that set of hypotheses to be recycled and passed on to the other set of hypotheses and that set can be retested, if necessary, at a 2-sided alpha level of 0.05.

Figure 7: Multiplicity Testing Strategy for Trials PS0002 and PS0005



Source: page 23 of the SAPs for Trials PS0002 and PS0005

For Trial PS0003, the protocol specified a sequential gatekeeping approach, see Table 10. For Step 13, non-inferiority is demonstrated if the lower bound of the 95% CI for the difference is greater than -10% (etanercept minus Cimzia 400 mg). For Step 14, there are two comparisons: (1) Cimzia 400 mg vs. etanercept for superiority and (2) Cimzia 200 mg vs. etanercept for non-inferiority. To control the Type I error rate within this step, the protocol specified using the Hochberg method:

- If (1) is significant in demonstrating superiority at a 2-sided α = 0.05 and (2) is significant in demonstrating non-inferiority 95% CI for the difference and 10% non-inferiority margin, then both (1) and (2) are deemed statistically significant and can proceed to Step 15.
- If (1) is <u>not</u> significant at the 2-sided α = 0.05 and (2) is significant in demonstrating non-inferiority based on lower bound of the 97.5% CI for the

difference and 10% non-inferiority margin, then only (2) is deemed statistically significant and the testing procedure is concluded (i.e., do not proceed to Step 15).

- If (1) is significant in demonstrating superiority at a 2-sided α = 0.025 and (2) is not significant in demonstrating non-inferiority 95% CI for the difference and 10% non-inferiority margin, then only (1) is deemed statistically significant and the testing procedure is concluded (i.e., do not proceed to Step 15).
- If (1) is not significant in demonstrating superiority at a 2-sided α = 0.05 and (2) is not significant in demonstrating non-inferiority 95% CI for the difference and 10% non-inferiority margin, then neither (1) or (2) are deemed statistically significant and the testing procedure is concluded (i.e., do not proceed to Step 15).

Table 10: Multiplicity Testing Strategy for Trial PS0003

		Comparison			
Order	**Endpoint**	**Cimzia 400 mg vs. Placebo**	**Cimzia 200 mg vs. Placebo**	**Cimzia 400 mg vs. Etanercept**	**Cimzia 200 mg vs. Etanercept**
1	PASI 75 at Week 12	Superiority			
2	PASI 75 at Week 12		Superiority		
3	PGA of 0 or 1 at Week 12	Superiority			
4	PGA of 0 or 1 at Week 12		Superiority		
5	PASI 90 at Week 12	Superiority			
6	PASI 90 at Week 12		Superiority		
7	PASI 75 at Week 16	Superiority			
8	PASI 75 at Week 16		Superiority		
9	PGA of 0 or 1 at Week 16	Superiority			
10	PGA of 0 or 1 at Week 16		Superiority		
11	PASI 90 at Week 16	Superiority			
12	PASI 90 at Week 16		Superiority		
13	PASI 75 at Week 12			Non-Inferiority	
14	PASI 75 at Week 12			Superiority	Non-Inferiority
15	PASI 75 at Week 12				Superiority

The protocol-specified primary method for handling binary missing data is the multiple imputation (MI) approach, where the missing data is imputed using the Markov Chain Monte Carlo (MCMC) method. For each treatment arm, the protocol specified imputing the missing data 75 times. For the primary efficacy endpoints (all binary), the protocol specified the following sensitivity analyses for handling of missing data:

1. Impute missing data as non-responders (i.e., failures).
2. Impute missing data using the MI approach, where the missing data is imputed using a logistic regression model with factors for treatment group, pooled center, and prior biologics exposure.

For the continuous secondary endpoint (i.e., change from baseline in DLQI at Week 16 for Trials PS0002 and PS0005), the protocol specified imputing missing data using the last observation carried forward (LOCF) approach.

7.2.3. Subject Disposition, Demographics and Baseline Disease Characteristics

Trial PS0002 enrolled and randomized a total of 227 subjects from 21 investigational sites. Trial PS0005 enrolled and randomized a total of 234 subjects from 30 investigational sites. Trial PS0003 enrolled and randomized a total of 559 subjects from 64 investigational sites. Table 11 presents the disposition of subjects during the first 16 weeks of Trials PS0002 and PS0005. Table 12 presents the disposition of subjects during the first 16 weeks of Trial PS0003. In all three trials, the discontinuation rates were higher in the placebo arm compared to the two Cimzia arms. In addition, the discontinuation rates were slightly lower for Cimzia 400 mg arm compared to the Cimzia 200 mg arm in all three trials.

Table 11: Disposition of Subjects through Week 16 for Trials PS0002 and PS0005

	Trial PS0002			Trial PS0005		
	Cimzia			Cimzia		
	400 mg (N=87)	200 mg (N=91)	Placebo (N=49)	400 mg (N=88)	200 mg (N=95)	Placebo (N=51)
Discontinued	4 (5%)	7 (8%)	4 (8%)	1 (1%)	3 (3%)	5 (10%)
Adverse Event	1	3	0	1	0	0
Lost to Follow-Up	0	2	1	0	0	1
Other	2	0	0	0	1	1
Subject's Request	1	2	3	0	2	3

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

Table 12: Disposition of Subjects through Week 16 for Trial PS0003

	Cimzia			
	400 mg (N=167)	200 mg (N=165)	Etanercept (N=170)	Placebo (N=57)
Discontinued	5 (3%)	6 (4%)	11 (6%)	2 (4%)
Adverse Event	1	1	4	0
Lack of Efficacy	0	0	1	0
Lost to Follow-Up	2	1	2	1
Other	1	1	1	0
Protocol Violation	0	0	1	0
Subject's Request	1	3	2	1

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

Table 13 presents the demographics and baseline disease characteristics for Trials PS0002 and PS0005. Table 14 presents the demographics and baseline disease characteristics for Trial PS0003. The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and were similar between each trial. Trials PS0002 and PS0005 had higher proportion of subjects from the United States compared to Trial PS0003.

Table 13: Demographics and Baseline Disease Characteristics for Trials PS0002 and PS0005

Characteristic		Trial PS0002			Trial PS0005		
		Cimzia			Cimzia		
		400 mg (N=87)	200 mg (N=91)	Placebo (N=49)	400 mg (N=88)	200 mg (N=95)	Placebo (N=51)
Age (years)	Mean (SD)	46 (14)	47 (13)	43 (14)	44 (12)	45 (13)	48 (13)
	Median	45	47	43	44	43	48
	Range	21 to 72	20 to 75	20 to 73	21 to 65	21 to 76	21 to 71
	< 65	76 (87%)	84 (92%)	46 (94%)	86 (98%)	90 (95%)	45 (88%)
	≥ 65	11 (13%)	7 (8%)	3 (6%)	2 (2%)	5 (5%)	6 (12%)
Sex	Male	43 (49%)	58 (64%)	26 (53%)	60 (68%)	67 (71%)	35 (69%)
	Female	44 (51%)	33 (36%)	23 (47%)	28 (32%)	28 (29%)	16 (31%)
Race	White	81 (93%)	86 (95%)	44 (90%)	79 (90%)	87 (92%)	45 (88%)
	Black	3 (3%)	3 (3%)	1 (2%)	3 (3%)	2 (2%)	3 (6%)
	Asian	3 (3%)	0	3 (6%)	2 (2%)	3 (3%)	2 (4%)
	Other	0	2 (2%)	1 (2%)	4 (5%)	3 (3%)	1 (2%)
Weight (kg)	Mean (SD)	91.8 (27.7)	97.8 (25.6)	87.1 (26.4)	92.2 (21.7)	92.6 (21.0)	95.2 (19.5)
	Median	86	96.6	82.6	88.6	91	92
	Range	45.3 to 197.5	49.0 to 174.5	47.0 to 188.9	56.8 to 168.2	48.0 to 153.7	54.7 to 140.0
	≤ 90 kg	50 (57%)	39 (43%)	33 (67%)	48 (55%)	44 (46%)	23 (45%)
	> 90 kg	37 (43%)	52 (57%)	16 (33%)	40 (45%)	51 (54%)	28 (55%)
Prior Biologic Therapy	Yes	30 (34%)	32 (35%)	14 (29%)	29 (33%)	30 (32%)	15 (29%)
	No	57 (66%)	59 (65%)	35 (71%)	59 (67%)	65 (68%)	36 (71%)
Country	U.S.	38 (44%)	37 (41%)	22 (45%)	30 (34%)	31 (33%)	17 (33%)
	Non-U.S.	49 (56%)	54 (59%)	27 (55%)	58 (66%)	64 (67%)	34 (67%)
PGA	3 - Moderate	61 (70%)	66 (73%)	37 (76%)	65 (74%)	62 (65%)	35 (69%)
	4 - Severe	26 (30%)	25 (27%)	12 (24%)	23 (26%)	33 (35%)	16 (31%)
PASI	Mean (SD)	19.5 (6.7)	18.4 (5.9)	17.3 (5.3)	19.6 (7.9)	20.0 (8.2)	19.8 (7.5)
	Median	17.9	16.4	15.2	18.0	17.2	17.4
	Range	12.2 to 56.0	11.7 to 42.4	12.0 to 32.8	11.6 to 68.6	12.0 to 53.0	12.0 to 44.9
Percent BSA	Mean (SD)	23.1 (11.6)	21.4 (12.2)	20.0 (9.5)	24.1 (16.6)	25.4 (16.9)	26.1 (16.1)
	Median	20	17	17	19	20	19
	Range	10 to 81	10 to 77	10 to 46	10 to 96	10 to 80	10 to 85

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

Table 14: Demographics and Baseline Disease Characteristics for Trial PS0003

Characteristic		Cimzia 400 mg (N=167)	Cimzia 200 mg (N=165)	Etanercept (N=170)	Placebo (N=57)
Age (years)	Mean (SD)	45 (12)	47 (14)	45 (14)	47 (13)
	Median	45	48	44.5	49
	Range	18 to 75	19 to 80	18 to 78	20 to 69
	< 65	156 (93%)	153 (93%)	157 (92%)	53 (93%)
	≥ 65	11 (7%)	12 (7%)	13 (8%)	4 (7%)
Sex	Male	107 (64%)	113 (68%)	127 (75%)	34 (60%)
	Female	60 (36%)	52 (32%)	43 (25%)	23 (40%)
Race	White	162 (97%)	158 (96%)	163 (96%)	57 (100%)
	Black	2 (1%)	2 (1%)	3 (2%)	0
	Asian	3 (2%)	3 (2%)	1 (1%)	0
	Other	0	2 (1%)	3 (2%)	0
Weight (kg)	Mean (SD)	86.3 (20.0)	89.7 (20.6)	88.6 (20.7)	93.7 (29.7)
	Median	83.2	86.0	86.4	89.9
	Range	41.8 to 152.0	49.0 to 171.1	49.0 to 170.0	55.0 to 198.5
	≤ 90 kg	112 (67%)	99 (60%)	101 (59%)	29 (51%)
	> 90 kg	55 (33%)	66 (40%)	69 (41%)	28 (49%)
Prior Biologic Therapy	Yes	48 (29%)	44 (27%)	51 (30%)	11 (19%)
	No	119 (71%)	121 (73%)	119 (70%)	46 (81%)
Country	U.S.	27 (16%)	26 (16%)	29 (17%)	10 (18%)
	Non-U.S.	140 (84%)	139 (84%)	141 (83%)	47 (82%)
PGA	3 - Moderate	113 (68%)	114 (69%)	115 (68%)	40 (70%)
	4 - Severe	54 (32%)	51 (31%)	55 (32%)	17 (30%)
PASI	Mean (SD)	20.8 (7.7)	21.4 (8.8)	21.0 (8.2)	19.1 (7.1)
	Median	18.8	18.5	18.6	16.8
	Range	12.0 to 58.5	12.0 to 55.5	11.2 to 48.0	12.0 to 43.1
Percent BSA	Mean (SD)	27.6 (15.3)	28.1 (16.7)	27.5 (15.5)	24.3 (13.8)
	Median	24.0	23.0	21.0	20.0
	Range	10 to 89	10 to 84	10 to 82	10 to 74

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

7.2.4. Results for the Primary and Secondary Efficacy Endpoints

Table 15 presents the results for the for the co-primary and secondary efficacy endpoints at Week 16 for Trials PS0002 and PS0005 in the RS population. Table 16 presents the results for the primary and secondary efficacy endpoints against placebo for Trial PS0003 in the RS population. For all of the efficacy endpoints presented in Table 15 and Table 16, both doses of Cimzia were statistically superior to placebo (p-values < 0.001). The results for the PPS population (not shown) were very similar to those in the RS population.

Table 15: Results of the Co-Primary and Secondary Endpoints at Week 16 for Trials PS0002 and PS0005 (RS[1])

		Trial PS0002			Trial PS0005		
		Cimzia			Cimzia		
		400 mg (N=87)	200 mg (N=91)	Placebo (N=49)	400 mg (N=88)	200 mg (N=95)	Placebo (N=51)
Co-Primary Endpoints	**PGA of 0 or 1 (MI[2])**						
	Rate[3]	65%	61%	3%	55%	45%	4%
	Model-Based Rate[4]	72%	67%	2%	58%	47%	4%
	P-Value[4]	<0.001	<0.001	--	<0.001	<0.001	--
	PASI 75 (MI[2])						
	Rate[3]	82%	81%	13%	75%	65%	7%
	Model-Based Rate[4]	83%	81%	12%	76%	67%	7%
	P-Value[4]	<0.001	<0.001	--	<0.001	<0.001	--
Secondary Endpoints	**PASI 90 (MI[2])**						
	Rate[3]	52%	50%	5%	44%	36%	0%
	Model-Based Rate[4]	55%	53%	5%	44%	36%	0%
	P-Value[4]	<0.001	<0.001	--	<0.001	<0.001	--
	Change from baseline in DLQI (LOCF[5])	N=87	N=90	N=49	N=86	N=93	N=48
	Mean	-10.0	-11.1	-2.9	-9.6	-8.9	-3.3
	LS Mean[6]	-10.0	-10.4	-3.8	-10.2	-9.3	-3.3
	P-Value[6]	<0.001	<0.001	--	<0.001	<0.001	--

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)
(1) Randomized Set (RS): all randomized subjects.
(2) Missing data was imputed using the multiple imputation (MI) approach.
(3) Rate displayed is the average of the 75 imputed datasets.
(4) Rate and p-value are based on logistic regression with factors for treatment, region, and prior biologic exposure (yes/no).
(5) Missing data was imputed using the last observation carried forward (LOCF).
(6) LS mean and p-value are based on ANCOVA with factors for treatment, region, and prior biologic exposure (yes/no).

Table 16: Results of the Primary and Secondary Endpoints Against Placebo for Trial PS0003 (RS[1], MI[2])

		Cimzia®		
		400 mg (N=167)	200 mg (N=165)	Placebo (N=57)
Primary Endpoint	**PASI 75 at Week 12**			
	Rate[3]	69%	63%	5%
	Model-Based Rate[4]	67%	61%	5%
	P-Value[4]	<0.001	<0.001	--
Secondary Endpoints	**PGA of 0 or 1 at Week 12**			
	Rate[3]	54%	43%	2%
	Model-Based Rate[4]	50%	40%	2%
	P-Value[4]	<0.001	<0.001	--
	PASI 90 at Week 12			
	Rate[3]	34%	31%	0%
	Model-Based Rate[4]	34%	31%	0%
	P-Value[4]	<0.001	<0.001	--
	PASI 75 at Week 16			
	Rate[3]	75%	69%	4%
	Model-Based Rate[4]	75%	68%	4%
	P-Value[4]	<0.001	<0.001	--
	PGA of 0 or 1 at Week 16			
	Rate[3]	62%	52%	4%
	Model-Based Rate[4]	58%	48%	3%
	P-Value[4]	<0.001	<0.001	--
	PASI 90 at Week 16			
	Rate[3]	49%	40%	0%
	Model-Based Rate[4]	49%	40%	0%
	P-Value[4]	<0.001	<0.001	--

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)
(1) Randomized Set (RS): all randomized subjects.
(2) Missing data was imputed using the multiple imputation (MI) approach.
(3) Rate displayed is the average of the 75 imputed datasets.
(4) Rate and p-value are based on logistic regression with factors for treatment, region, and prior biologic exposure (yes/no).

For all three trials, the primary method for handling missing PGA and PASI data was multiple imputation (MI) approach where missing data is imputed using the MCMC method. The protocols for these trials specified the following two sensitivity analyses for the handling of missing data: (i) impute missing data using non-responder imputation and (ii) impute missing data using MI where missing data is imputed using a regression model with treatment, region and prior use of biologic therapy as factors in the model. Table 17 presents the number of subjects with missing PGA and PASI data at Week 16 along with the results for PGA response (i.e., PGA score of 0 or 1) and PASI 75 at Week 16 across the various imputation methods. Overall, the proportion of subjects with missing data at Week 16 was relatively low, and the proportion of subjects with missing data in the placebo arm was greater than the two Cimzia arms. For all three trials, the results for PGA response and PASI 75 at Week 16 were similar across various imputation methods.

Table 17: Results for PGA Response(1) and PASI 75 at Week 16 with Different Approaches for Handling Missing Data

	PGA Response			PASI 75		
	Cimzia			Cimzia		
Endpoints	**400 mg**	**200 mg**	**Placebo**	**400 mg**	**200 mg**	**Placebo**
Trial PS0002	**N=87**	**N=91**	**N=49**	**N=87**	**N=91**	**N=49**
Subjects with Missing Data	***3 (3%)***	***6 (7%)***	***4 (8%)***	***3 (3%)***	***6 (7%)***	***3 (6%)***
MI-MCMC(2) (Primary)	65%	61%	3%	82%	81%	13%
MI-Reg(3)	65%	62%	2%	82%	82%	14%
NRI(4)	63%	58%	2%	79%	77%	12%
Observed Cases	66%	62%	2%	82%	82%	13%
Trial PS0005	**N=88**	**N=95**	**N=51**	**N=88**	**N=95**	**N=51**
Subjects with Missing Data	***1 (1%)***	***3 (3%)***	***5 (10%)***	***1 (1%)***	***3 (3%)***	***5 (10%)***
MI-MCMC(2) (Primary)	55%	45%	4%	75%	65%	7%
MI-Reg(3)	55%	45%	4%	75%	66%	6%
NRI(4)	55%	44%	4%	74%	65%	6%
Observed Cases	55%	46%	4%	75%	67%	7%
Trial PS0003	**N=167**	**N=165**	**N=57**	**N=167**	**N=165**	**N=57**
Subjects with Missing Data	***5 (3%)***	***6 (4%)***	***2 (4%)***	***5 (3%)***	***6 (4%)***	***2 (4%)***
MI-MCMC(2) (Primary)	62%	52%	4%	75%	69%	4%
NRI(4)	61%	51%	4%	74%	67%	4%
Observed Cases	63%	53%	4%	77%	70%	4%

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Multiple imputation (MI) where missing data is imputed using the MCMC method. Rates displayed is the average of the 75 imputed datasets.
(3) Multiple imputation (MI) where missing data is imputed using regression model with factors for treatment, region, and prior biologic exposure (yes/no). Rates displayed is the average of the 75 imputed datasets.
(4) Missing data imputed using non-responder imputation (NRI).

Trial PS0003 included etanercept as an active comparator. Because the applicant did not establish an adequate scientific bridge between U.S. licensed Enbrel and EU approved etanercept, these products are considered distinct products for the purpose of this review. Table 18 presents the results for the secondary efficacy endpoint against etanercept (i.e., PASI 75 at Week 12) in the overall population (all sites) and by country (U.S. vs. Non-U.S.) for Trial PS0003. In the overall population, Cimzia 400 mg was statistically superior to etanercept (p-value = 0.015); however, Cimzia 200 mg was not statistically superior to etanercept in the overall population (p-value = 0.152). In the U.S., only subgroup, both doses of Cimzia were not statistically superior to etanercept (p-values ≥ 0.846).

Table 18: Results for the Secondary Endpoint Against Etanercept for Trial PS0003 (RS[1], MI[2])

Population	Endpoints	Cimzia 400 mg (N=167)	Cimzia 200 mg (N=165)	Etanercept (N=170)
Overall Populations (All Subjects)	**PASI 75 at Week 12**			
	Rate[2]	69%	63%	57%
	Model-Based Rate[3]	67%	61%	53%
	P-Value[3]	0.015	0.152	--
U.S. Subjects	**PASI 75 at Week 12**			
	Rate[2]	59%	60%	57%
	Model-Based Rate[3]	59%	59%	56%
	P-Value[3]	0.849	0.846	--
Non-U.S. Subjects	**PASI 75 at Week 12**			
	Rate[2]	70%	64%	55%
	Model-Based Rate[3]	69%	63%	54%
	P-Value[3]	0.011	0.143	--

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)
(1) Randomized Set (RS): all randomized subjects.
(2) Missing data was imputed using the multiple imputation (MI) approach.
(3) Rate displayed is the average of the 75 imputed datasets.
(4) Rate and p-value are based on logistic regression with factors for treatment, region, and prior biologic exposure (yes/no).

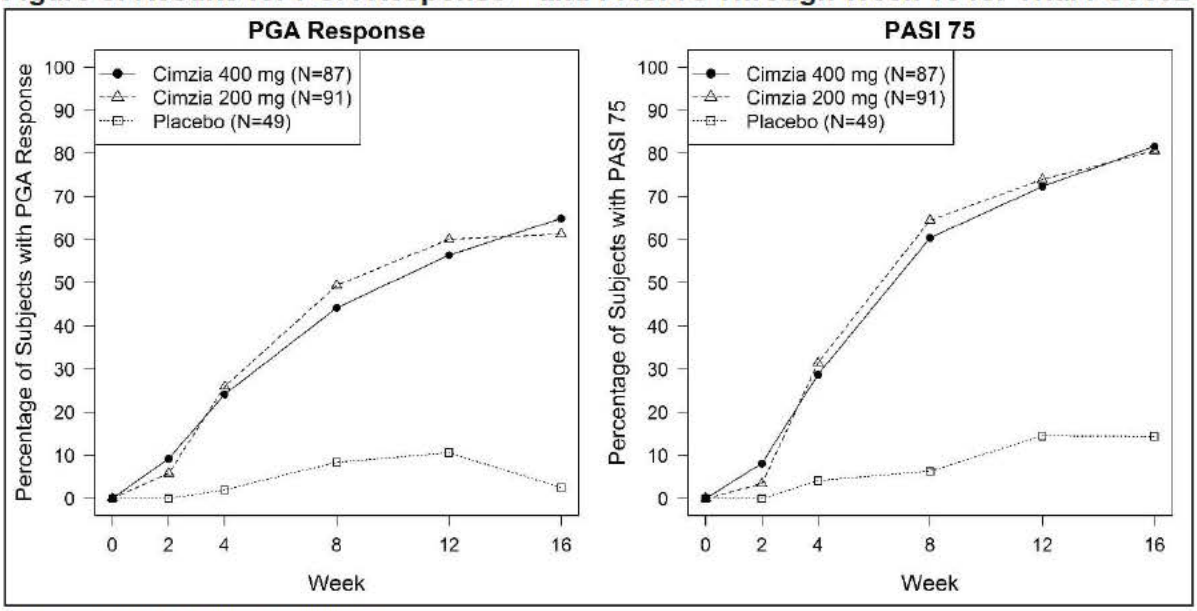
7.2.5. Patient Reported Outcomes (PROs)

The protocols for Trials PS0002, PS0005 and PS0003 included the assessment of patient reported outcomes (PROs). All three trials included the Dermatology Life Quality Index (DLQI), Work Productivity and Activity Impairment Questionnaire-Specific Health Problem (WPAI-SHP) questionnaire, the European Quality of Life 5 dimensions 3 levels (EQ-5D-3L) questionnaire, and the Short Form (36) Health Survey (SF-36). Trials PS0002 and PS005 also included the Hospital Anxiety and Depression Scale (HADS). All of the endpoints based on the PROs except DLQI (Trials PS0002 and PS0005) were designated as "other" endpoints and not included in the multiplicity testing strategy; therefore, these endpoints are considered exploratory and not included in this review. The results of DLQI for Trials PS0002 and PS0005 are presented in Section 7.2.4.

7.2.6. Efficacy Over Time

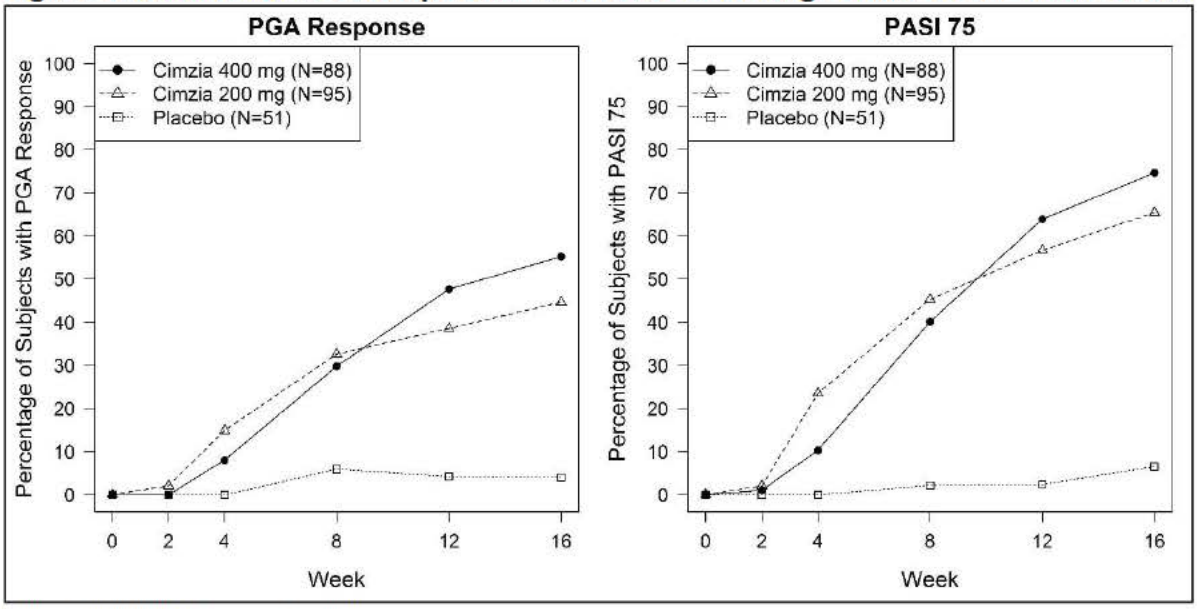
Figure 8, Figure 9 and Figure 10 present the results for PGA response and PASI 75 through Week 16 for Trials PS0002, PS0005 and PS0003, respectively.

Figure 8: Results for PGA Response[1] and PASI 75 Through Week 16 for Trial PS0002



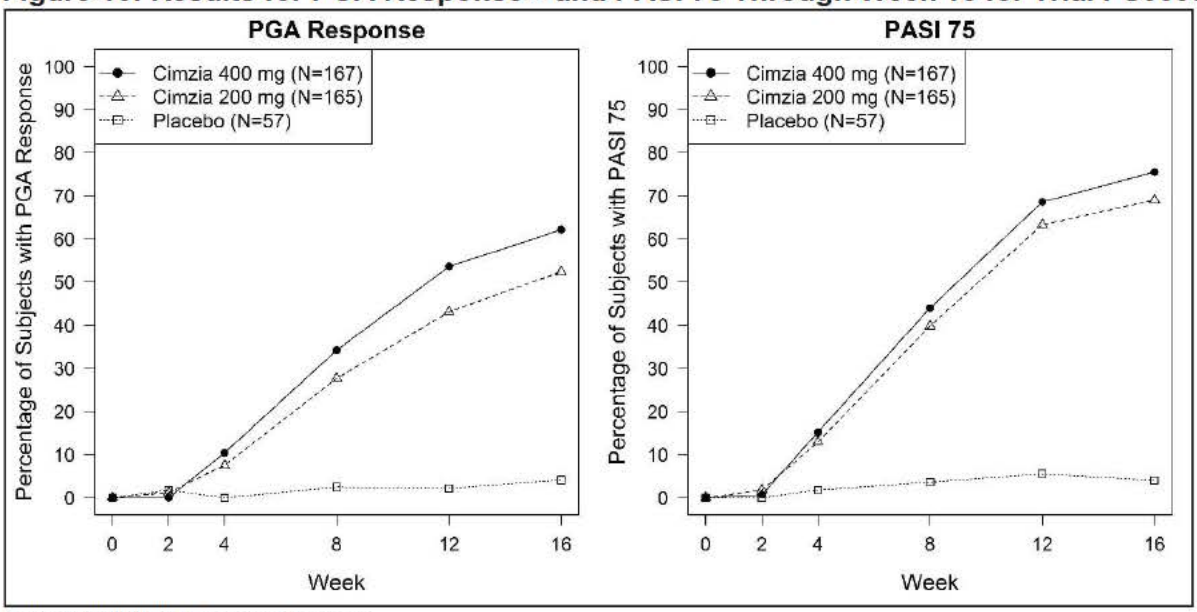
Source: Statistical Reviewer's Analysis
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Randomized Set (RS): all randomized subjects. Missing data was imputed using the multiple imputation (MI) approach. Rates displayed are the averages over the 75 imputed datasets.

Figure 9: Results for PGA Response[1] and PASI 75 Through Week 16 for Trial PS0005



Source: Statistical Reviewer's Analysis
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Randomized Set (RS): all randomized subjects. Missing data was imputed using the multiple imputation (MI) approach. Rates displayed are the averages over the 75 imputed datasets.

Figure 10: Results for PGA Response(1) and PASI 75 Through Week 16 for Trial PS0005



Source: Statistical Reviewer's Analysis
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Randomized Set (RS): all randomized subjects. Missing data was imputed using the multiple imputation (MI) approach. Rates displayed are the averages over the 75 imputed datasets.

Trials PS0002 and PS0005 evaluated continuous treatment of Cimzia 400 mg and 200 mg for 48 weeks. For Trial PS0003, subjects that were treated with Cimzia during the first 16 weeks and achieved PASI 75 at Week 16 were re-randomized as follows:

- Subjects initially randomized to Cimzia 200 mg Q2W were re-randomized in a 2:2:1 ratio to receive either Cimzia 200 mg Q2W, Cimzia 400 mg Q4W or placebo
- Subjects initially randomized to Cimzia 400 mg Q2W were re-randomized in a 2:2:1 ratio to receive either Cimzia 200 mg Q2W, Cimzia 400 mg Q2W or placebo

Table 19 presents the percentage of PGA responders and PASI 75 responders at Week 16 who were also responders at Week 48. It should be noted that the PGA responders at Week 16 for Trial PS0003 is a subset of the PASI 75 responders because the re-randomization at Week 16 was only based on PASI 75. For Trials PS0002 and PS0005, the applicant imputed missing data using the multiple imputation (MI) approach. This reviewer also assessed the response rates when missing data is imputed as non-responders, which is the approach the applicant used for Trial PS0003.

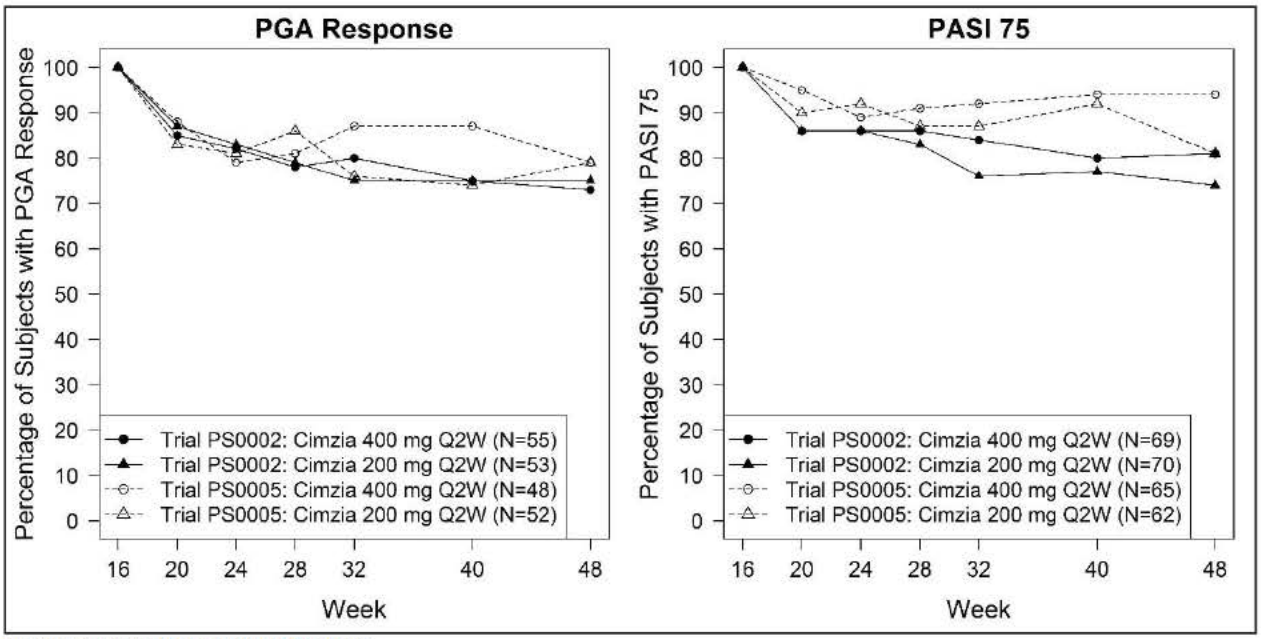
Figure 11 presents the response rates (PGA response and PASI 75) from Week 16 to 48 for subjects who were responders at Week 16 in Trials PS0002 and PS0005. Figure 12 presents the response rates for Trial PS0003.

Table 19: Response Rates at Week 48 for Responders at Week 16

	PGA score of 0 or 1 at Week 48		PASI 75 at Week 48	
	Rate[1]	Applicant's Model-Based[2] Rate	Rate[1]	Applicant's Model-Based[2] Rate
Trial PS0002				
400 mg Q2W → 400 mg Q2W	40/55 (73%)	85%	56/69 (81%)	96%
200 mg Q2W → 200 mg Q2W	40/53 (76%)	85%	52/70 (74%)	88%
Trial PS0005				
400 mg Q2W → 400 mg Q2W	38/48 (79%)	86%	61/65 (94%)	99%
200 mg Q2W → 200 mg Q2W	33/42 (79%)	82%	50/62 (81%)	86%
Trial PS0003				
400 mg Q2W → 400 mg Q2W	37/40 (93%)	NA	48/49 (98%)	NA
400 mg Q2W → 200 mg Q2W	28/42 (67%)	NA	40/50 (80%)	NA
400 mg Q2W → Placebo	3/18 (17%)	NA	9/25 (36%)	NA
200 mg Q2W → 200 mg Q2W	19/30 (63%)	NA	35/44 (80%)	NA
200 mg Q2W → 400 mg Q4W	29/36 (81%)	NA	39/44 (89%)	NA
200 mg Q2W → Placebo	3/16 (19%)	NA	10/22 (46%)	NA

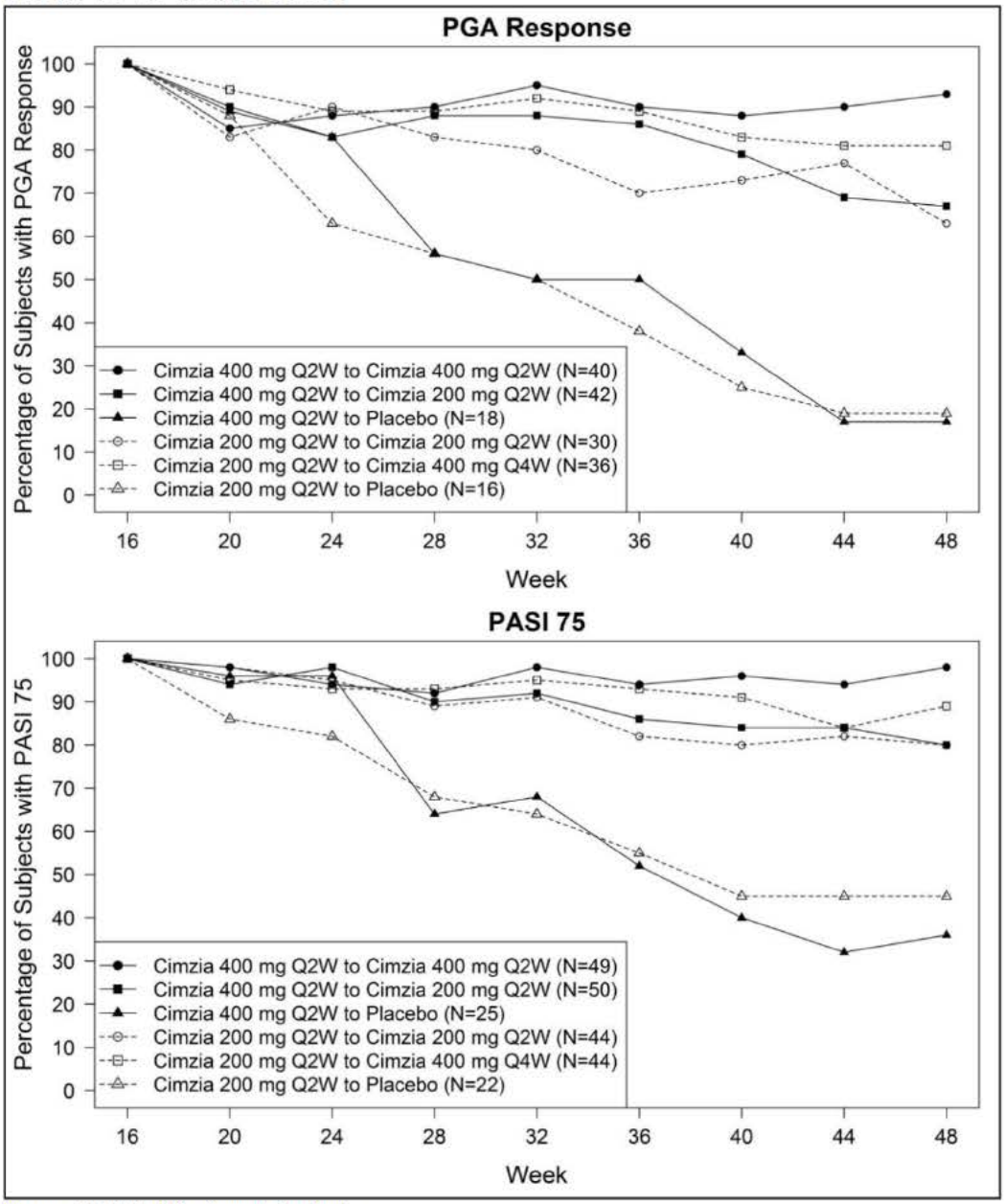
(1) Missing data imputed using non-responder imputation (NRI).
(2) Missing data imputed using multiple imputation (MI). Rate based on a logistic regression model with factors for treatment, region, and prior biologic exposure (yes/no).

Figure 11: Response Rates (PGA Response[1] and PASI 75) for Responders at Week 16 in Trials PS0002 and PS0005



Source: Statistical Reviewer's Analysis
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Missing data was imputed using non-responder imputation (NRI).

Figure 12: Response Rates (PGA Response[1] and PASI 75) for Responders at Week 16 in Trial PS0003



Source: Statistical Reviewer's Analysis
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Missing data was imputed using non-responder imputation (NRI).

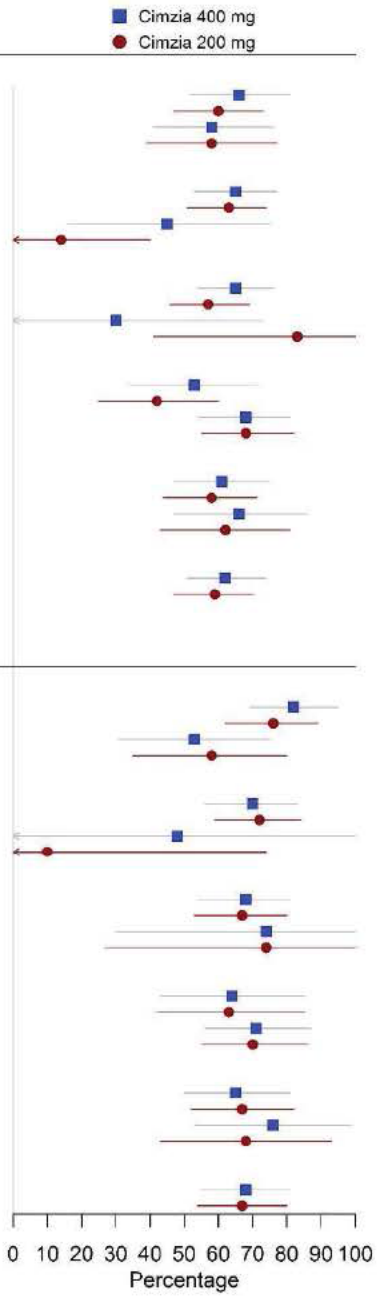
7.2.7. Findings in Special/Subgroup Populations

7.2.7.1. Sex, Age, Race, Prior Use of Biologics, and Prior Use of Systemic Therapy

Figure 13, Figure 14, and Figure 15 present the results for PGA response (i.e., PGA score of 0 or 1) and PASI 75 at Week 16 by sex, age (18-64 and 65+ years), race (White and Non-White), prior use of biologic therapy, and prior use of systemic therapy for Trials PS0002, PS0005 and PS0003, respectively. In all three trials, the majority of the subjects enrolled in the trials were white (approximately 94%) and of < 65 years of age (approximately 93%); therefore, it would be difficult to detect any differences in efficacy for the Non-White and ≥ 65 subgroups. For sex, the treatment effect was generally slightly higher in males compared to females.

Figure 13: PGA Response[1] and PASI 75 at Week 16 by Sex, Age, Race, Prior Biologic Therapy, and Prior Systemic Therapy for Trial PS0002

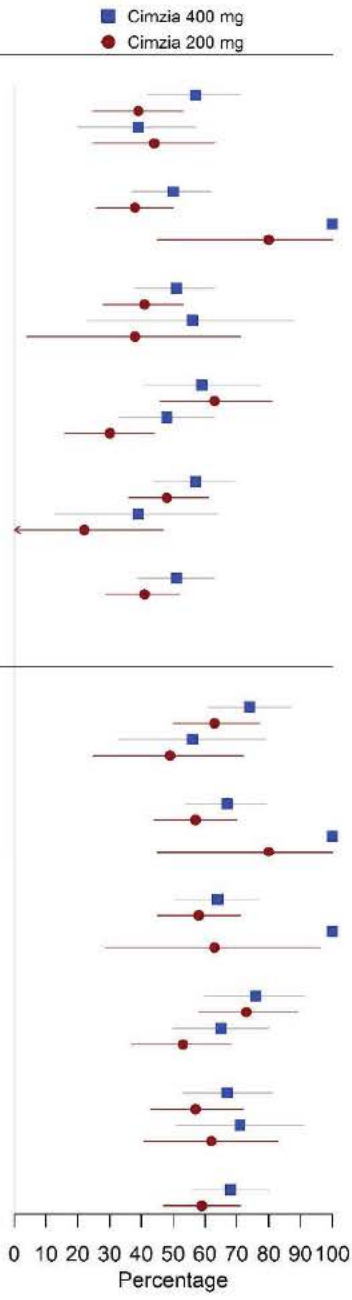
Subgroups (n[C400], n[C200], n[P])	Cimzia 400 mg (N=87)	Cimzia 200 mg (N=91)	Placebo (N=49)	Difference to Placebo Cimzia 400 mg	Difference to Placebo Cimzia 200 mg
PGA Response:					
Sex					
Males (43, 58, 26)	66%	60%	0%	66%	60%
Females (44, 33, 23)	64%	64%	5%	59%	59%
Age					
18-64 (76, 84, 46)	68%	65%	3%	65%	62%
65+ (11, 7, 3)	45%	14%	0%	45%	14%
Race					
White (81, 86, 44)	67%	60%	2%	65%	58%
Non-White (6, 5, 5)	33%	86%	3%	30%	83%
Prior Biologic Therapy					
Yes (30, 32, 14)	53%	42%	0%	53%	42%
No (57, 59, 35)	71%	72%	4%	67%	68%
Prior Systemic Therapy					
Yes (63, 65, 36)	64%	61%	3%	61%	58%
No (24, 26, 13)	67%	62%	0%	67%	62%
Overall	65%	61%	3%	62%	58%
PASI 75:					
Sex					
Males (43, 58, 26)	86%	80%	4%	82%	76%
Females (44, 33, 23)	77%	82%	24%	53%	58%
Age					
18-64 (76, 84, 46)	82%	84%	12%	70%	72%
65+ (11, 7, 3)	82%	43%	33%	49%	10%
Race					
White (81, 86, 44)	82%	80%	14%	68%	66%
Non-White (6, 5, 5)	83%	84%	10%	73%	74%
Prior Biologic Therapy					
Yes (30, 32, 14)	71%	71%	7%	64%	64%
No (57, 59, 35)	87%	86%	16%	71%	70%
Prior Systemic Therapy					
Yes (63, 65, 36)	78%	79%	12%	66%	67%
No (24, 26, 13)	92%	84%	16%	76%	68%
Overall	82%	81%	13%	69%	68%



Source: Statistical Reviewer's Analysis
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Randomized Set (RS): all randomized subjects. Missing data was imputed using the multiple imputation (MI) approach. Rates displayed are the averages over the 75 imputed datasets.

Figure 14: PGA Response(1) and PASI 75 at Week 16 by Sex, Age, Race, Prior Biologic Therapy, and Prior Systemic Therapy for Trial PS0005

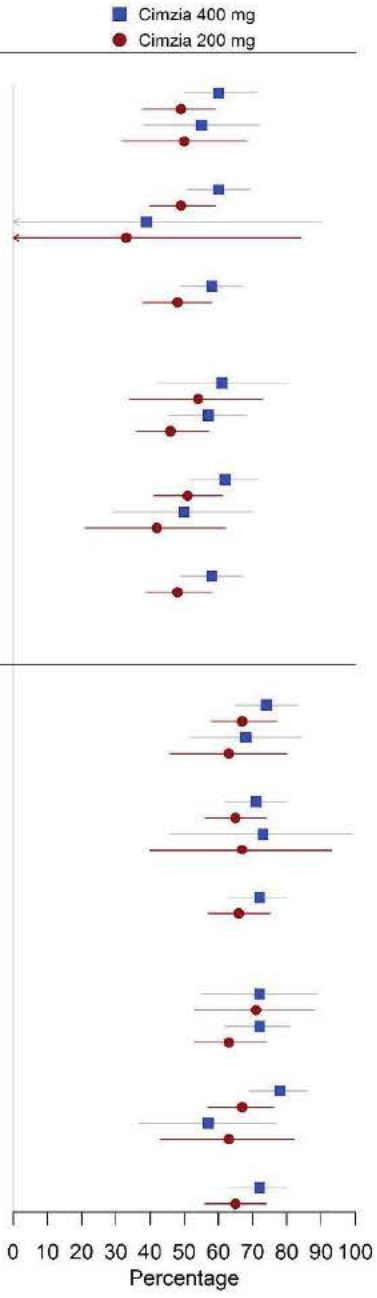
Subgroups (n[C400], n[C200], n[P])	Cimzia 400 mg (N=88)	Cimzia 200 mg (N=95)	Placebo (N=51)	Difference to Placebo Cimzia 400 mg	Difference to Placebo Cimzia 200 mg
PGA Response:					
Sex					
Males (60, 67, 35)	63%	45%	6%	57%	39%
Females (28, 28, 16)	39%	44%	0%	39%	44%
Age					
18-64 (86, 90, 45)	54%	43%	5%	49%	38%
65+ (2, 5, 6)	100%	80%	0%	100%	80%
Race					
White (79, 87, 45)	55%	45%	5%	50%	40%
Non-White (9, 8, 6)	56%	38%	0%	56%	38%
Prior Biologic Therapy					
Yes (29, 30, 15)	59%	63%	0%	59%	63%
No (59, 65, 36)	53%	36%	6%	47%	30%
Prior Systemic Therapy					
Yes (61, 66, 36)	57%	48%	0%	57%	48%
No (27, 29, 15)	52%	36%	13%	39%	23%
Overall	55%	45%	4%	51%	41%
PASI 75:					
Sex					
Males (60, 67, 35)	79%	69%	6%	73%	63%
Females (28, 28, 16)	64%	57%	8%	56%	49%
Age					
18-64 (86, 90, 45)	74%	65%	7%	67%	58%
65+ (2, 5, 6)	100%	80%	0%	100%	80%
Race					
White (79, 87, 45)	72%	66%	7%	65%	59%
Non-White (9, 8, 6)	100%	63%	0%	100%	63%
Prior Biologic Therapy					
Yes (29, 30, 15)	76%	73%	0%	76%	73%
No (59, 65, 36)	74%	62%	9%	65%	53%
Prior Systemic Therapy					
Yes (61, 66, 36)	73%	64%	6%	67%	58%
No (27, 29, 15)	78%	69%	7%	71%	62%
Overall	75%	65%	7%	68%	58%



Source: Statistical Reviewer's Analysis
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Randomized Set (RS): all randomized subjects. Missing data was imputed using the multiple imputation (MI) approach. Rates displayed are the averages over the 75 imputed datasets.

Figure 15: PGA Response[1] and PASI 75 at Week 16 by Sex, Age, Race, Prior Biologic Therapy, and Prior Systemic Therapy for Trial PS0003

Subgroups (n[C400], n[C200], n[P])	Cimzia 400 mg (N=167)	Cimzia 200 mg (N=165)	Placebo (N=57)	Difference to Placebo: Cimzia 400 mg	Difference to Placebo: Cimzia 200 mg
PGA Response:					
Sex					
Males (107, 113, 34)	61%	50%	1%	60%	49%
Females (60, 52, 23)	64%	59%	9%	55%	50%
Age					
18-64 (156, 153, 53)	62%	52%	3%	59%	49%
65+ (11, 12, 4)	64%	58%	25%	39%	33%
Race					
White (162, 158, 57)	62%	52%	4%	58%	48%
Non-White (5, 7, 0)	65%	57%	NA	NA	NA
Prior Biologic Therapy					
Yes (48, 44, 11)	64%	57%	3%	61%	54%
No (119, 121, 46)	61%	51%	4%	57%	47%
Prior Systemic Therapy					
Yes (123, 118, 39)	63%	52%	1%	62%	51%
No (44, 47, 18)	61%	53%	11%	50%	42%
Overall	62%	52%	4%	58%	48%
PASI 75:					
Sex					
Males (107, 113, 34)	75%	68%	1%	74%	67%
Females (60, 52, 23)	77%	71%	9%	68%	62%
Age					
18-64 (156, 153, 53)	75%	69%	4%	71%	65%
65+ (11, 12, 4)	73%	67%	0%	73%	67%
Race					
White (162, 158, 57)	76%	70%	4%	72%	66%
Non-White (5, 7, 0)	68%	57%	NA	NA	NA
Prior Biologic Therapy					
Yes (48, 44, 11)	74%	73%	2%	72%	71%
No (119, 121, 46)	76%	68%	4%	72%	64%
Prior Systemic Therapy					
Yes (123, 118, 39)	78%	67%	1%	77%	66%
No (44, 47, 18)	68%	74%	11%	57%	63%
Overall	75%	69%	4%	71%	65%



Source: Statistical Reviewer's Analysis
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Randomized Set (RS): all randomized subjects. Missing data was imputed using the multiple imputation (MI) approach. Rates displayed are the averages over the 75 imputed datasets.

7.2.7.2. Baseline Weight and Baseline Disease Severity

Table 20 presents the results of PGA response and PASI 75 by baseline PGA score and baseline weight. For Trial PS0002, the treatment effect for both doses of Cimzia in subjects with a baseline PGA score of 3 (moderate) was higher compared to subjects with a baseline PGA score of 4 (severe); however, for Trial PS0005, the reverse trend was observed (i.e., the treatment effect was higher in subjects with a baseline PGA score of 4). For Trial PS0003, the treatment effect for Cimzia 400 mg was higher in subjects with a baseline PGA score of 3 (moderate); however, the treatment effect for Cimzia 200 mg was higher in subjects with a baseline PGA score of 4 (severe). For baseline weight, the treatment effect was generally higher in subjects with a baseline weight ≤ 90 kg compared to those with a baseline weight > 90 kg.

Table 21 presents the results for PGA response and PASI 75 by both baseline PGA score and baseline weight together. For subjects with baseline PGA score of 3 (moderate) and baseline weight ≤ 90 kg, the treatment effect for Cimzia 200 mg was similar to Cimzia 400 mg (i.e., the treatment effect for Cimzia 200 mg was greater than or equal to the treatment effect of Cimzia 400 mg in 5 out of the 6 comparisons).

Table 20: PGA Response(1) and PASI 75 at Week 16 by Baseline PGA Score and Baseline Weight

	PGA Score of 0 or 1					PASI 75				
	Cimzia			Treatment Effect (Δ)		Cimzia			Treatment Effect (Δ)	
	400 mg	200 mg	Placebo	400 mg	200 mg	400 mg	200 mg	Placebo	400 mg	200 mg
Trial PS0002										
Baseline PGA Score										
3 - Moderate (61, 66, 37)	72%	69%	3%	68%	66%	85%	85%	15%	70%	70%
4 - Severe (26, 25, 12)	49%	41%	0%	49%	41%	75%	70%	8%	66%	61%
Baseline Weight										
≤ 90 kg (50, 39, 33)	77%	73%	4%	74%	69%	90%	91%	14%	76%	77%
> 90 kg (37, 52, 16)	48%	53%	0%	48%	53%	70%	73%	13%	58%	61%
Trial PS0005										
Baseline PGA Score										
3 - Moderate (65, 62, 35)	55%	44%	6%	49%	38%	73%	61%	7%	67%	55%
4 - Severe (23, 33, 16)	57%	45%	0%	57%	45%	78%	73%	6%	72%	67%
Baseline Weight										
≤ 90 kg (48, 44, 23)	56%	53%	5%	52%	48%	73%	73%	6%	67%	67%
> 90 kg (40, 51, 28)	54%	37%	4%	50%	34%	77%	59%	7%	69%	52%
Trial PS0003										
Baseline PGA Score										
3 - Moderate (113, 114, 40)	64%	63%	6%	58%	57%	73%	75%	6%	67%	70%
4 - Severe (54, 51, 17)	59%	28%	0%	59%	28%	81%	55%	0%	81%	55%
Baseline Weight										
≤ 90 kg (112, 99, 29)	68%	64%	5%	63%	59%	79%	74%	8%	71%	67%
> 90 kg (55, 66, 28)	50%	35%	4%	47%	31%	69%	61%	0%	69%	61%

Source: Statistical Reviewer's Analysis
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Randomized Set (RS): all randomized subjects. Missing data was imputed using the multiple imputation (MI) approach. Rates displayed are the averages over the 75 imputed datasets.

Table 21: PGA Response[1] and PASI 75 at Week 16 by Both Baseline PGA Score and Baseline Weight

	PGA Score of 0 or 1					PASI 75				
	Cimzia			Treatment Effect (Δ)		Cimzia			Treatment Effect (Δ)	
	400 mg	200 mg	Placebo	400 mg	200 mg	400 mg	200 mg	Placebo	400 mg	200 mg
Trial PS0002										
Baseline PGA Score and Weight										
3 - Moderate										
≤ 90 kg (33, 30, 27)	82%	85%	5%	77%	80%	91%	91%	17%	74%	74%
> 90 kg (28, 36, 10)	60%	56%	0%	60%	56%	77%	80%	10%	67%	70%
4 - Severe										
≤ 90 kg (17, 9, 6)	69%	33%	0%	69%	33%	88%	89%	0%	88%	89%
> 90 kg (9, 16, 6)	11%	45%	0%	11%	45%	49%	59%	17%	32%	42%
Trial PS0005										
Baseline PGA Score and Weight										
3 - Moderate										
≤ 90 kg (38, 32, 20)	58%	51%	5%	53%	46%	68%	69%	7%	62%	62%
> 90 kg (27, 30, 15)	50%	37%	7%	44%	30%	80%	53%	7%	74%	47%
4 - Severe										
≤ 90 kg (10, 12, 3)	50%	58%	0%	50%	58%	90%	83%	0%	90%	83%
> 90 kg (13, 21, 13)	62%	38%	0%	62%	38%	69%	67%	8%	61%	59%
Trial PS0003										
Baseline PGA Score and Weight										
3 - Moderate										
≤ 90 kg (78, 70, 19)	66%	74%	7%	59%	67%	76%	79%	12%	64%	67%
> 90 kg (35, 44, 21)	59%	46%	5%	54%	41%	66%	69%	0%	66%	69%
4 - Severe										
≤ 90 kg (34, 29, 10)	73%	40%	0%	73%	40%	84%	62%	0%	84%	62%
> 90 kg (20, 22, 7)	35%	14%	0%	35%	14%	75%	45%	0%	75%	45%

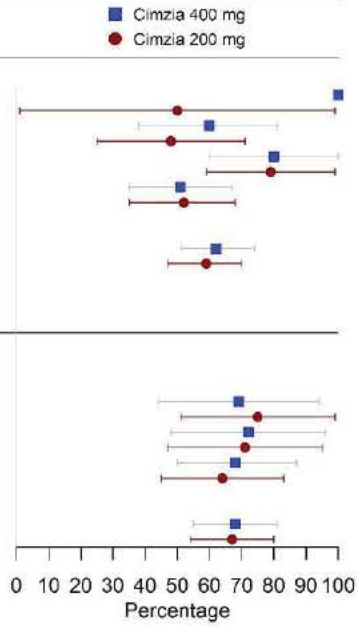
Source: Statistical Reviewer's Analysis
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Randomized Set (RS): all randomized subjects. Missing data was imputed using the multiple imputation (MI) approach. Rates displayed are the averages over the 75 imputed datasets.

7.2.7.3. Geographic Location (Country)

Trial PS0002 was conducted in 4 countries (i.e., Austria, Canada, Poland, and the United States). Trial PS0005 was conducted in 5 countries (i.e., Canada, Czech Republic, Germany, Hungary, and the United States). Trial PS0003 was conducted in 9 countries (i.e., Bulgaria, Czech Republic, France, Germany, Hungary, Netherlands, Poland, the United Kingdom, and the United States). Figure 16, Figure 17, and Figure 18 present the results for PGA response and PASI 75 at Week 16 by country for Trials PS0002, PS0005, and PS0003, respectively. Across the three trials, the treatment effect varied across the countries; however, this this may be due to the relatively small sample sizes in many of the countries.

Figure 16: PGA Response(1) and PASI 75 at Week 16 by Country for Trial PS0002

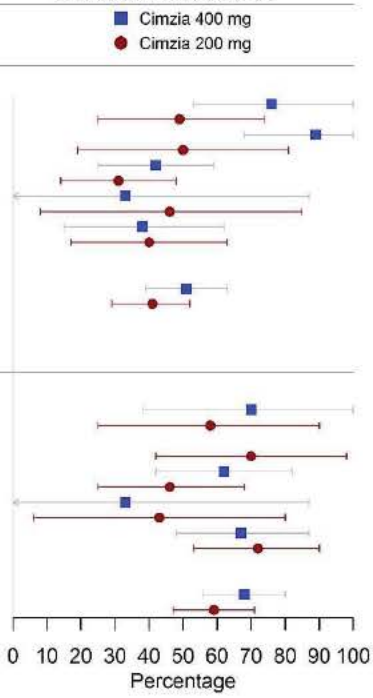
Subgroups (n[C400], n[C200], n[P])	Cimzia 400 mg (N=87)	Cimzia 200 mg (N=91)	Placebo (N=49)	Difference to Placebo Cimzia 400 mg	Difference to Placebo Cimzia 200 mg
PGA Response:					
Country					
Austria (2, 4, 1)	100%	50%	0%	100%	50%
Canada (23, 24, 13)	61%	50%	1%	60%	49%
Poland (24, 26, 13)	88%	87%	8%	80%	79%
United States (38, 37, 22)	51%	52%	0%	51%	52%
Overall	65%	61%	3%	62%	58%
PASI 75:					
Country					
Austria (2, 4, 1)	100%	75%	100%	0%	-25%
Canada (23, 24, 13)	80%	86%	11%	69%	75%
Poland (24, 26, 13)	88%	86%	15%	73%	71%
United States (38, 37, 22)	78%	73%	10%	68%	63%
Overall	82%	81%	13%	69%	68%



Source: Statistical Reviewer's Analysis
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Randomized Set (RS): all randomized subjects. Missing data was imputed using the multiple imputation (MI) approach. Rates displayed are the averages over the 75 imputed datasets.

Figure 17: PGA Response[1] and PASI 75 at Week 16 by Country for Trial PS0005

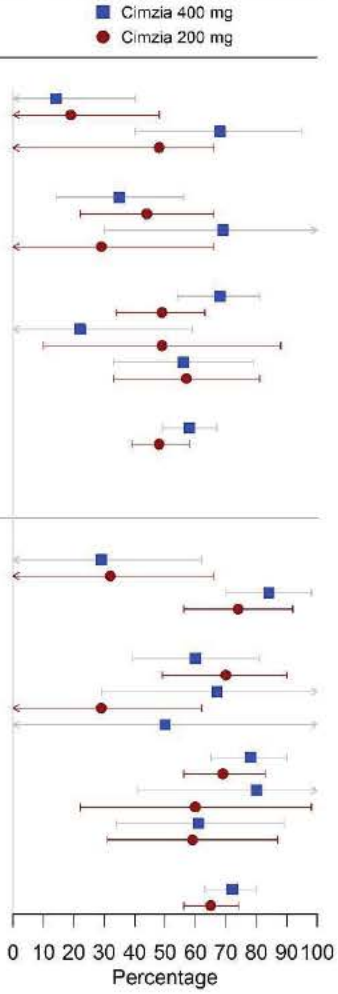
Subgroups (n[C400], n[C200], n[P])	Cimzia 400 mg (N=88)	Cimzia 200 mg (N=95)	Placebo (N=51)	Difference to Placebo Cimzia 400 mg	Difference to Placebo Cimzia 200 mg
PGA Response:					
Country					
Canada (15, 18, 9)	77%	50%	1%	76%	49%
Czech Republic (9, 10, 5)	89%	50%	0%	89%	50%
Germany (31, 29, 17)	42%	31%	0%	42%	31%
Hungary (3, 7, 3)	33%	46%	0%	33%	46%
United States (30, 31, 17)	50%	52%	12%	38%	40%
Overall	55%	45%	4%	51%	41%
PASI 75:					
Country					
Canada (15, 18, 9)	84%	72%	15%	69%	57%
Czech Republic (9, 10, 5)	100%	70%	0%	100%	70%
Germany (31, 29, 17)	68%	52%	6%	62%	46%
Hungary (3, 7, 3)	33%	43%	0%	33%	43%
United States (30, 31, 17)	73%	77%	6%	67%	71%
Overall	75%	65%	7%	68%	58%



Source: Statistical Reviewer's Analysis
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Randomized Set (RS): all randomized subjects. Missing data was imputed using the multiple imputation (MI) approach. Rates displayed are the averages over the 75 imputed datasets.

Figure 18: PGA Response(1) and PASI 75 at Week 16 by Country for Trial PS0003

Subgroups (n[C400], n[C200], n[P])	Cimzia 400 mg (N=167)	Cimzia 200 mg (N=165)	Placebo (N=57)	Difference to Placebo Cimzia 400 mg	Difference to Placebo Cimzia 200 mg
PGA Response:					
Country					
Bulgaria (7, 8, 3)	14%	19%	0%	14%	19%
Czech Republic (25, 23, 8)	80%	61%	13%	67%	48%
France (3, 4, 2)	100%	100%	0%	100%	100%
Germany (20, 21, 5)	35%	44%	0%	35%	44%
Hungary (6, 7, 2)	69%	29%	0%	69%	29%
Netherlands (2, 0, 1)	100%	NA	100%	0%	NA
Poland (71, 69, 23)	72%	53%	4%	68%	49%
United Kingdom (6, 7, 3)	22%	49%	0%	22%	49%
United States (27, 26, 10)	59%	60%	3%	56%	57%
Overall	62%	52%	4%	58%	48%
PASI 75:					
Country					
Bulgaria (7, 8, 3)	29%	32%	0%	29%	32%
Czech Republic (25, 23, 8)	84%	74%	0%	84%	74%
France (3, 4, 2)	100%	100%	0%	100%	100%
Germany (20, 21, 5)	60%	70%	0%	60%	70%
Hungary (6, 7, 2)	67%	29%	0%	67%	29%
Netherlands (2, 0, 1)	50%	NA	0%	50%	NA
Poland (71, 69, 23)	82%	74%	4%	78%	70%
United Kingdom (6, 7, 3)	80%	60%	0%	80%	60%
United States (27, 26, 10)	74%	72%	13%	61%	59%
Overall	75%	69%	4%	71%	65%



Source: Statistical Reviewer's Analysis
(1) Response is defined as a PGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(2) Randomized Set (RS): all randomized subjects. Missing data was imputed using the multiple imputation (MI) approach. Rates displayed are the averages over the 75 imputed datasets.

7.3. Review of Safety

7.3.1. Safety Review Approach

The primary review of safety of certolizumab pegol (certolizumab) for the treatment of moderate to severe plaque psoriasis focused on the evaluation of pooled data from 3 trials, Trials PS0005, PS0002, and PS0003. These Phase 3 trials were similar with regard to design, study population, dosing regimen, and key primary and secondary endpoints. The study designs were identical for the initial treatment period (Week 0 to Week 16) except that Trial PS0003 included an active-comparator arm (etanercept) and a primary efficacy endpoint measurement (PASI 75) at Week 12 and secondary efficacy endpoint measurements at Week 16 (including, PASI 75 and PGA). In all three trials, the initial treatment period included a placebo comparator.

In the pooled safety database from Phase 3 trials, 667 subjects were treated with the proposed certolizumab dosing regimen of 400mg every other week, administered SC, including 114 subjects who were treated for at least 48 weeks.

The analysis of the safety database (Trials PS0005, PS0002, and PS0003) was conducted for the following groups.

1. Placebo-controlled period: Week 0-16
    - Placebo
    - Certolizumab 200mg
    - Certolizumab 400mg
    - All certolizumab (200mg and 400mg)

2. All certolizumab exposed group: (W0-144) of studies C87040, C87044, PS0005, PS0002, and PS0003.

The applicant is not proposing labeling for plaque psoriasis to include comparison to etanercept. Thus, the data regarding etanercept was not included in the safety analysis. The sample sizes by treatment group are summarized below.

Table 22: Subject Population, Placebo-Controlled Safety Period (Trials PS0005, PS0002, and PS0003)

Trial	Treatment Group	# of Subjects
PS0005	Certolizumab 400mg	87
	Certolizumab 200mg	91
	Placebo	49
PS0002	Certolizumab 400mg	88
	Certolizumab 200mg	95
	Placebo	51
PS0003	Certolizumab 400mg	167
	Certolizumab 200mg	165
	Placebo	57
	Etanercept	159
Total	Certolizumab 400mg	342
	Certolizumab 200mg	351
	Placebo	157
	Etanercept	159

Source: Reviewer's own based on ISS and SUR.

The applicant submitted supportive safety data from the Phase 2 trials C87040 and C87044. This data was not pooled with the safety data from Trials PS0005, PS0002, and PS0003 for the analysis of adverse events compared to placebo because Trial C87040 had a different dosing regimen (200mg dosing group had a single 400mg loading dose at Week 0 and 12 week treatment period) and Trial C87044 was an open-label extension study design.

The safety data from the Phase 2 trials C87040 and C87044 were pooled with the safety data from Trials PS0005, PS0002, and PS0003 for analysis of potential serious adverse events, adverse events of special interest, and treatment-emergent adverse events.

The review team analyzed the following types of pooled data: exposure, demographic and baseline characteristics, prior psoriasis therapies, treatment emergent adverse events (TEAEs), serious AEs (SAEs), and AEs leading to discontinuation. The applicant identified adverse events of special interest (AESI) which included serious infections including opportunistic infections, malignancies, congestive heart failure, demyelinating-like disorders, cytopenias, serious bleeding events, lupus and lupus-like illness, serious skin reaction, and psoriasis.

7.3.2. Review of the Safety Database

Overall Exposure

In Phase 2 trial C87040, 117 subjects were treated with certolizumab for 12 weeks. Subjects who responded to treatment (PASI 75 or more) at week 12 who then relapsed (reduction by more than 50% of the maximal improvement in PASI score from baseline

during the treatment period) within 24 weeks after the last dose were eligible for re-treatment in Phase 2 study C87044. Seventy-one subjects from Trial C87040 enrolled in Study C87044 for re-treatment, receiving the same dose as in Trial C87040.

In the Phase 3 trials (PS0005, PS0002, and PS0003), 850 subjects were randomized to receive placebo or certolizumab. By the end of the Phase 3 trials, 995 subjects were treated with certolizumab. This number includes:

- Subjects who received treatment with certolizumab only
- Subjects who were crossed over from placebo to certolizumab in Trials PS0005, PS0002, and PS0003
- Subjects who were crossed over from etanercept to certolizumab in Trial PS0003

Of the total 1112 certolizumab-treated subjects in the Phase 2 and Phase 3 Trials, 905 subjects were exposed for up to 6 months, and 779 subjects exposed for up to 12 months. More than half of the subjects (677/995, 68%) treated with certolizumab in Phase 3 trials received the proposed dose of 400mg SC every other week for at least 16 weeks. In the Phase 3 trials, 703 subjects received doses of 200mg SC every other week for at least 16 weeks (including 44 subjects from Trial PS0003 who crossed over from certolizumab 200mg every other week to 400mg every 4 weeks during Week 16-48). The average number of administrations was 32.7 across the Phase 2 and Phase 3 psoriasis trials.

Through the end of the reporting period in the pooled safety analysis set (Trials PS0005, PS0002, and PS0003), a total of 995 subjects received at least 1 injection of certolizumab. A total of 562 subjects were treated for at least 48 weeks. This safety database is sufficient to evaluate the safety of certolizumab for the proposed indication in the target population.

In the Safety Update Report, the applicant reported a total exposure of 1481.3 subject-years to certolizumab during Phase 2 and 3 trials, which included data up to the clinical cut date of June 30, 2017. The subject exposure is summarized in the table below.

Table 23: Summary of Duration of Exposure during Phase 2 and 3 Trials

	6 months	12 months	18 months	24 months
All Certolizumab	906	779	551	66
Certolizumab 400mg	542	273	95	9
Certolizumab 200mg	558	334	184	23

Source: Safety Update Report, Table 4.3, modified.

- Durations are cumulative through study
- Subjects receiving 400mg every 4 weeks were counted as subjects receiving 200mg every other week.
- This includes subjects who crossed over to certolizumab after beginning treatment with etanercept.

In addition, the applicant submitted safety information regarding exposure to certolizumab for subjects enrolled in Phase 3 trial for psoriatic arthritis. Inclusion criteria required a psoriatic skin lesion or a documented history of psoriasis. A total of 273 subjects were exposed to certolizumab in this study.

Relevant characteristics of the safety population:

Demographic characteristics of the subject population in the certolizumab development program are presented in greater detail in Section 7.2.3 (subject disposition) of this review. A brief summary of demographic information relevant to the evaluation of safety will be presented here.

In Phase 3 Trials PS0005, PS0002, and PS0003, the subjects were mostly White (94%) and male (63.8%). The median age was 45.7 years (range 18-80 years), and 59.8% were age 40-64 years. The demographic characteristics were similar for the subjects enrolled in Phase 2 trials C87040 and C87044, with the exception of the geographic region because the Phase 2 trials were conducted in France and Germany. Demographic characteristics were comparable across treatment groups in all 5 trials. Across these 5 trials, 53/809 (6.6%) subjects treated with certolizumab were 65 years of age or older.

In Trials PS0005, PS0002, and PS0003, baseline disease characteristics were consistent with a patient population with moderate to severe psoriasis and were similar across treatment groups. The median PASI score was 17.5, 69.9% had a PGA score of 3 and 30.1% had a PGA score of 4, and the median BSA involved was 20.3%. The mean weight of subjects was 90 kg (41.8-198.5 kg). Among all randomized subjects in Trial C87040, the mean PASI score was 21, the mean BSA involved was 28.4%, 51.5% of subjects had an IGA=3, and 33.5% of subjects had an IGA=4.

In Trials PS0005, PS0002, and PS0003, the medical histories of the trial population were similar in incidences across treatment groups. The most frequently reported conditions and diseases by preferred term were:

- Hypertension in 29.4%
- Psoriatic arthropathy in 17.6%
- Obesity in 11.9%

In Trials PS0005, PS0002, and PS0003, 53% of subjects had received prior phototherapy and 40.9% had received prior nonbiologic systemic therapy. A total of 9.5% had received >1 such treatment previously. A total of 30.8% had received prior treatment with a biologic, and 13.3% had received prior anti-TNF treatment. A total of 28.5% of subjects in Trials PS0005, PS0002, and PS0003 had never received prior treatment with systemic nonbiologic or biologic therapies. In Trial C87040, 69.9% of subjects had received previous phototherapy, 79% previously received systemic therapy, and 23.3% previously received anti-TNF therapy. The histories of prior treatment were similar between treatment groups in Trials C87040, C87044, PS0005, PS0002, and PS0003.

Adequacy of the safety database:

The total subject exposure to certolizumab 400mg SC every other week and certolizumab 400mg SC Week 0, 2, and 4 followed by 200mg every other week for up to 144 weeks, provides adequate data for the evaluation of safety. The demographics of the study population are sufficiently representative of the target population. Therefore, the safety database presented by the applicant is sufficient to characterize the safety profile of certolizumab for the treatment of moderate to severe plaque psoriasis.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of certolizumab. Data quality and fitness were evaluated. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the applicant.

Categorization of Adverse Events

For the Phase 3 pooled safety analysis set, the applicant defined an adverse event (AE) as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment." This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. At each visit, in addition to investigator self-assessment procedures, a general prompt will be used to detect AEs

- "Did you notice anything unusual about your health (since your last visit)?

AEs were categorized by system-organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. The coding of adverse events in the BLA submission appeared adequate and allowed for accurate estimation of AE risks.

Investigators monitored each subject regularly for AEs or serious AE (SAEs) occurring throughout the trial. AEs and SAEs were recorded and reported from the time of signed and dated Informed Consent Form (ICF) was obtained until completion of the subject's last study-related procedure (which may have included contact for follow-up of safety). Investigators categorized AE for seriousness, intensity, causality, duration, and action taken with study drug. All AEs or SAEs were followed until satisfactory resolution or stable level of sequelae is achieved, investigator no longer deems the AE clinically significant, until 10 weeks after subjects has discontinued investigational drug product, or until the patient is lost to follow-up. Serious adverse events, including those spontaneously reported to the investigator within 10 weeks after the last dose of study drug, were to be reported using the Serious Adverse Event Form.

A serious medical event (SAE) was defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically important
- Pregnancy results in miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure, ectopic pregnancy, fetal demise, or any infant congenital anomaly/birth defect.
- Overdose resulting in associated clinical signs or symptoms
- Adverse events of special interests

The following AEs were required to be reported immediately:

- SAE
- Suspected transmission of an infectious agent via a medicinal product
- AE of special interest

The following AEs were considered adverse events of special interest (AESI):

- Serious infections including opportunistic infections
- Malignancies including lymphoma
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia and leucopenia
- Serious bleeding events
- Lupus and lupus-like illness
- Serious skin reactions (e.g., Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

For the analysis of AEs, the applicant allocated the subject to the treatment group based on initial randomization.

The definition of AE, TEAE, and SAE are acceptable. The classification system used by investigators to describe the severity of AE as well as the causal relationship between AE and study product are also acceptable. The applicant's identification and presentation of AE of special interest was appropriate.

Routine Clinical Tests

In Trials PS0005, PS0002, and PS0003, the evaluation of safety was conducted during visits to the clinic. In Trials PS0005 and PS0002, scheduled visits occurred at Screening, Baseline (Week 0), then every 2 weeks Week 2-48, then every 12 weeks Week 48-144. In Trial PS0003, scheduled visits occurred at Screening, Baseline (Week 0), Week 1, Week 2, then every 2 weeks Week 2-48, Week 52, Week 60, then every 12 weeks Week 60-144. The evaluation of safety included clinical laboratory tests, vital signs, physical examinations, and evaluation for TB. These will be discussed in more detail below. Safety monitoring also included recording of adverse events, which was discussed in the previous section.

Clinical laboratory evaluation included the following:

- Hematology (hemoglobin, hematocrit, red blood cell [RBC] count, mean cell volume, mean corpuscular hemoglobin concentration, mean cell hemoglobin concentration, white blood cell [WBC] count, lymphocytes, atypical lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelet count), serum chemistry (alanine aminotransferase, aspartate aminotransferase, creatinine kinase, total bilirubin, urea, calcium, chloride, creatinine, glucose, potassium, magnesium, sodium, total cholesterol, lactate dehydrogenase, and gamma-glutamyl transferase), and urinalysis (albumin, bacteria, crystals, glucose, pH, RBC, and WBC): Screening, Baseline/Week 0, every 4 weeks Week 4-16, every 8 weeks Week 24-48, and every 12 weeks Week 60-144.
- Hepatitis B and C, and HIV antibody test (PS0005 and PS0002: Czech Republic, Germany, and Canada; PS0003: Czech Republic, Germany, France, and United Kingdom): Screening
- Pregnancy testing: serum only at Screening, urine and serum at Baseline, Week 48, Week 144/Completion, and Follow-Up Visit 10 weeks after last dose
- Height, pulse rate, and temperature: Screening
- Blood pressure: Baseline, Screening, Week 2, every 4 weeks Week 4- 32, Week 40, and 48, and every 12 weeks Week 60-144. In PS0003, Baseline, Screening, Week 1 and 2, every 4 weeks Week 4-52, and every 12 weeks Week 64-144.
- Weight: Baseline, Screening, Week 16, and Week 48
- Physical examinations: Screening; Baseline; and Week16, 48, 96 (PS0005 and PS0002) or 100 (PS0003), and 144.

At screening, subjects were evaluated for latent and active tuberculosis (TB) by chest x-ray and IGRA tuberculosis test. IGRA tuberculosis test was also conducted at Week 48, 96 (PS0005 and PS0002) or 100 (PS0003), and 144.

7.3.4. Safety Results

Deaths

Six deaths were reported across the 5 trials in the development program until the cut date for the Safety Update Report (June 30, 2017). None of the deaths occurred during the Phase 3 placebo-controlled period, and no death was assessed as causally related to study product. The table below summarizes the deaths that occurred during the plaque psoriasis development program.

Table 24: Deaths during the Certolizumab Development Program for Plaque Psoriasis

Trial Study product (initial/maint[1])	Study Day of fatal AE/days of Cert[2] treatment	Subject number	Narrative
C87044 cert 400mg Q2W	18 wks after last dose of study drug/56	(b) (6)	A 72-year-old man died of cerebral hemorrhage 18 weeks after last dose of study drug. No autopsy was conducted.
PS0005 cert 400mg Q2w/ cert 400mg Q2W	126/126	(b) (6)	A 41-year-old White man involved in a motor vehicle accident died on the scene of multiple injuries (PT=polytrauma), during the Maintenance Treatment Period. No autopsy was conducted.
PS0002 plb[3]/ cert 200mg Q2W	191/5	(b) (6)	A 66-year-old man was hospitalized for an SAE of abnormal blood count 5 days after a single dose of certolizumab 200mg during the Maintenance Treatment Period. The subject died 191 days after the single dose with no cause of death specified.
PS0002 cert 400mg Q2W/ cert 400mg Q2W	574 /574	(b) (6)	A 38-year-old White woman with a history of morbid obesity, hepatic steatosis, and gastritis experienced SAEs of disseminated intravascular coagulation, hemorrhagic necrotic pancreatitis, hepatic failure, hypovolemic shock, hepatic failure, jaundice, and cardiac arrest during the Open-Label Period. Autopsy recorded cause of death as cardiac arrest due to rapidly expanding liver failure and hypovolemic shock in the course of the hemorrhagic pancreatic necrosis. 81 days after last study drug dose. Applicant review identified laboratory and clinical findings suggestive of alcoholic fatty liver disease, though alcohol abuse could not be ascertained. Progression of nonalcoholic fatty liver disease linked to morbid obesity also a potential etiology of deterioration.
PS0003 etn[4]/ escape cert 400mg Q2W	377/264	(b) (6)	A 70-year-old White woman involved in a motor vehicle accident who was hospitalized with traumatic brain injury (PT=craniocerebral injury) during the Open-Label Period. She was unconscious on admission and intubated. Autopsy supported conclusion of death due to traumatic injuries.
PS0003 cert 200mg Q2W/ cert 400mg Q4W	392/392	(b) (6)	A 71-year-old White woman experienced severe pneumonia during the Maintenance Treatment Period and was diagnosed with COPD during hospitalization. After discharge, the subject was admitted to the ICU 145 later for SAEs of pneumonia and COPD and died 18 days later. Unknown if autopsy conducted.

Source: Reviewer's own based on ISS and SUR.
[1]: maint=maintenance
[2]: cert=certolizumab
[3]: p b=placebo
[4]: etn=etanercept

Serious Adverse Events

In the pooled safety analysis set (PS0005, PS0002, and PS0003), serious adverse events (SAEs) were analyzed for the placebo-controlled treatment period (Week 0-16) and all certolizumab exposed subjects (Week 0-144). This analysis does not include data from subjects treated with etanercept in PS0003.

During the placebo-controlled period of the pooled Phase 3 trials (Trial PS0005, PS0002, and PS0003), the overall incidence of SAEs was 3% for subjects who received certolizumab, 4.7% for subjects who received certolizumab 400mg, 1.4% for subjects who received certolizumab 200mg, and 4.5% for subjects who received placebo.

Osteoarthritis was the only PT reported by more than 1 subject, (both subjects were in the certolizumab 400mg group). No SOC had an incidence of SAEs >1% in any treatment group (see table below). Most SAEs were assessed as not related to study drug. Drug-related SAEs were reported for 3 subjects in the certolizumab 400mg group (1 each for lymphadenitis, injection site reaction, and anaphylactoid reaction) and one subject in the certolizumab 200mg group (depression). See Section 7.3.5 Analysis of Submission-Specific Safety Issues and Section 7.3.8 Additional Safety Explorations for additional information regarding these events.

Table 25: Phase 3 Trials: SAEs reported during the Placebo-Controlled Period by SOC and PT (Selected SOCs with more than 1 subject)

Body System or Organ Class	Preferred Term	Cert[1] 400mg N=342 n (%)	Cert 200mg N=350 n (%)	All Cert N=692 n (%)	Placebo N=157 n (%)
Blood & lymphatic system	Lymphadenitis	1 (0.3)	0	1 (0.1)	0
	Splenic hematoma	0	1 (0.3)	1 (0.1)	0
Gastrointestinal	Abdominal pain	1 (0.3)	0	1 (0.1)	0
	Gastrointestinal necrosis	0	1 (0.3)	1 (0.1)	0
General disorders & administration site	Nodule	1 (0.3)	0	1 (0.1)	0
	Injection site reaction	1 (0.3)	0	1 (0.1)	0
	Strangulated hernia	0	1 (0.3)	1 (0.1)	0
Infections & infestations	Pneumonia	1 (0.3)	0	1 (0.1)	0
	Hematoma infection	1 (0.3)	0	1 (0.1)	0
	Abdominal abscess	1 (0.3)	0	1 (0.1)	0
Injury, poisoning & procedural	Contusion	1 (0.3)	0	1 (0.1)	0
	Concussion	1 (0.3)	0	1 (0.1)	0
	Lower limb fracture	1 (0.3)	0	1 (0.1)	0
	Rib fracture	0	1 (0.3)	1 (0.1)	0
Investigations	Chest X-ray abnormal	1 (0.3)	0	1 (0.1)	0
	Transaminases increased	0	1 (0.3)	1 (0.1)	0
Musculoskeletal & connective tissue	Osteoarthritis	2 (0.6)	0	2 (0.3)	0
	Polymyalgia rheumatica	0	1 (0.3)	1 (0.1)	0
Psychiatric	Bipolar I disorder	1 (0.3)	0	1 (0.1)	0
	Hallucination	0	1 (0.3)	1 (0.1)	0
	Depression	0	1 (0.3)	1 (0.1)	0

Source: Reviewer's Table using JReview.
[1]: cert=certolizumab

Exposure-adjusted incidence rates of SAEs during the placebo-controlled period were 15.61 per 100 subject years (subj yrs) in the certolizumab 400mg group, 4.73 per 100 subj yrs in the certolizumab 200mg group, 10.08 per subj yrs in the all certolizumab exposed group, and 15.4 in the placebo group. The certolizumab 400mg group had a similar exposure-adjusted incidence rate to the placebo group.

Exposure-adjusted incidence rates of SAEs for the all certolizumab exposed group across Phase 2 and 3 trials reported in the Safety Update Report are listed below.

Table 26: Exposure-adjusted Incidence Rates for Serious Adverse Events (Selected SOCs) for all Subjects Exposed to Certolizumab during Phase 2 and 3 Trials

Treatment Group	Cert[1] 400mg n (EAIR[2])	Cert 200mg n (EAIR)	All Cert Phase 3 n (EAIR)	All Cert Phase 2/3 n (EAIR)
Any Serious Adverse Event	67 (10.47)	55 (7.72)	120 (8.98)	127 (9.06)
Any Adverse Event (AE)	520 (185.27)	504 (160.90)	813 (173.24)	899 (181.08)
Any AE leading to drug discontin.	37 (5.57)	26 (3.53)	62 (4.43)	66 (4.49)

Source: Modified from Safety Update Report, Module 5.3.5.3, Table 5.3.3, p73; Table 5.3.4, p 577; and Table 5.3.5, 681.
[1]: cert=certolizumab
[2]: EAIR=exposure-adjusted incidence rate, events per 100 subject years
[3]: includes subject exposure of treatment arm cert 200mg Q2W/cert 400mg Q4W.

Reviewer's comment: There appears to be an imbalance in the exposure-adjusted incidence rates of SAEs between the certolizumab 400mg group and the certolizumab 200mg group. Whether the rates of SAEs were dependent on the received dose was difficult to ascertain given that during the trials subjects received different doses and dosing regimens as they crossed over between placebo, certolizumab 200mg Q2W, certolizumab 400mg Q4W, and certolizumab 400mg Q2W, and due the long half-life of the product (14 days).

Pregnancy-related SAE

Pregnancy was not reported as a SAE, while pregnancies resulting in miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure, ectopic pregnancy, fetal demise, or any infant congenital anomaly/birth defect were reported as SAEs.

In Phase 2/3 trials, 9 pregnancies were reported in 8 female subjects during Phase 2 and 3 trials (PS0005 – 1, PS0002 – 2, PS0003 - 3, and C87040 - 3 [two events occurred in one subject, 1 treatment-emergent and 1 post-treatment]). The Safety Update Report did not identify additional pregnancies. Four subjects experienced pregnancy-related SAEs. See table below for summary of pregnancies that occurred during Phase 2 and 3 trials.

Table 27: Summary of Subjects Who Reported Pregnancy during the Phase 2 and 3 Trials

Trial/Study product	Days of Cert[1] Treatment	Subject number	Narrative
C87040 cert 400mg Q2W	38	(b) (6)	A 21-year-old woman became pregnant while receiving study drug (due to missed doses and infrequent dosing of oral contraceptive) and underwent an induced abortion 8 weeks after her last menstrual period. Study medication was temporarily discontinued and **SAE** of pregnancy was reported. Second pregnancy reported during post-treatment period.
C87040 cert 400mg Q2W	43	(b) (6)	A 35-year-old woman became pregnant while receiving study drug and on oral contraceptives. The subject underwent elective termination approximately 7 weeks after her last menstrual period. Study medication was temporarily discontinued and subject remained in study.
PS0005 cert 400mg Q2W/ cert 400mg Q2W	125	(b) (6)	25-year-old White woman with a history of 2 normal pregnancies and 1 spontaneous abortion became pregnant while non-compliant with contraception. Study drug was stopped. Outcome of pregnancy unknown at time of data lock ((b) (6)).
PS0002 cert 400mg Q2W/ cert 400mg Q2W	334	(b) (6)	27-year-old White woman became pregnant while receiving study drug and attributed to contraception failure (condom, spermicide). Study drug was stopped. Outcome of pregnancy unknown at time of data lock ((b) (6)).
PS0002 cert 400mg Q2W/ cert 400mg Q2W	503	(b) (6)	42-year-old Black or African American woman became pregnant while receiving study drug and attributed to contraception failure (condom). Study drug was stopped. Outcome of pregnancy unknown at time of data lock ((b) (6)).
PS0003 cert 400mg Q2W/ cert 200mg Q2W	270	(b) (6)	A 38-year-old White woman became pregnant while receiving study drug and attributed to contraception failure (intrauterine device). Study drug was stopped and the subject discontinued due to a **SAE** of pregnancy. The expected delivery was (b) (6) (data lock for narrative (b) (6))
PS0003 cert 400mg Q2W/ cert 200mg Q2W	491	(b) (6)	A 27-year-old White woman with a history of previous spontaneous abortion, smoking (10 cigarettes per day), leukocytosis, and neutrophilia became pregnant while receiving study drug and attributed to contraception failure (oral contraceptives). Fourteen days after the positive pregnancy test, she experienced an event of missed abortion. Study medication was withdrawn and the subject discontinued for **SAE** of pregnancy.
PS0003 plb[2] Q2W/ cert 400mg Q2W	301	(b) (6)	A 32-year-old White woman with a history of two normal pregnancies and 2 stillbirths became pregnant while receiving study drug and attributed to contraception failure (condom rupture). Her last menstrual period was (b) (6). She underwent induced abortion on (b) (6). Study medication was withdrawn and the subject discontinued for **SAE** of pregnancy.

Source: Reviewer's own based on ISS and SUR narratives.
[1]: cert=certolizumab
[2]: p b=placebo

Selected narratives of serious adverse events

The following SAEs were assessed by the investigator as related to the study product and resulted in discontinuation from the trial:

- **SAE pulmonary embolism and intracardiac mass**: 39-year-old White man (PS0003: (b) (6)) with a medical history including cocaine sniffing (20 years previous) and smoking was admitted to the hospital following development of a heart murmur, increased white blood cells count, and positive blood cultures. Imaging identified a 5cm hyperechoic mass originating from the proximal part of the inferior vena cava suggestive of right atrial myxoma or vegetation. CT of the chest with ultrasound showed pulmonary embolism. The subject was empirically started on intravenous antibiotics, and after evaluation by cardiology and infectious disease specialists, a consensus determined the cardiac findings not due to endocarditis. Heparin drip and Coumadin were started and the subject was discharged with a diagnosis of pulmonary embolism and right atrial mass. The adverse events of intracardiac mass and pulmonary embolism were assessed as severe and not related to the study product. The study drug was withdrawn and the subject discontinued from the study.

- **SAE hypertensive crisis**: A 75-year-old White man (PS0003: (b) (6)) with a history of hypothyroidism, gastroesophageal reflux disease, diabetes mellitus, hypertension (since 2000), and headache experienced a mild, non-serious adverse event of uncontrolled hypertension that was assessed as not related to study drug and did not result in study drug withdrawal. During the Open-Label period, the subject experienced non-serious AEs of dyspnea and fatigue that was assessed as moderate and not related to study drug. Two months later, the subject was hospitalized for blood pressure greater than 220/100mmHg with shortness of breath, dyspnea on exertion, and fatigue. The investigator reported a SAE of hypertensive crisis of moderate intensity and not related to study drug. The study drug was withdrawn and the subject discontinued from the study.

Refer to Section 7.3.4 Safety Results “Deaths,” above for discussion of subjects who experienced SAEs that resulted in death.

Refer to Section 7.3.5 Analysis of Submission-Specific Safety Issues for discussion of subjects who discontinued the study product due to serious adverse events that were adverse events of special interest.

Dropouts and/or Discontinuations Due to Adverse Effects

During the placebo-controlled period, the number of subjects who discontinued trial medication due to adverse events was 1.2% in the certolizumab 400mg group, 1.1% in the certolizumab 200mg group, and 0% in the placebo group. In the certolizumab 400mg group, 4 subjects reported 7 AEs that lead to discontinuation (anaphylactoid reaction, eczema, dry skin, papular rash, cervical pain, exacerbation of psoriasis, and

pregnancy). In the certolizumab 200mg group, 4 subjects reported 5 AEs leading to discontinuation (pruritus generalized, dizziness, ALT increased, transaminases increased, and worsening depression).

In the Phase 3 trials, the rate of discontinuations due to AEs was 5.57 per 100 subject years (subj yrs) in the certolizumab 400mg group, 3.53 per 100 subj yrs in the certolizumab 200mg group, and 2.57 per 100 subj-yrs for the placebo group. The SOC of Skin and Subcutaneous Tissue Disorders had the highest number of discontinuations. In subjects receiving certolizumab, 14 subjects (0.99 per 100 subj yrs) discontinued the trial due to an event of skin disorder. These included preferred terms of generalized erythrodermic psoriasis, pustular palmoplantar psoriasis, exacerbation of psoriasis (3 subjects), worsening of plaque psoriasis, and guttate psoriasis.

Refer to Section 7.3.4 Safety Results “Serious Adverse Events” for selected narratives for subjects who discontinued the study product due to adverse events of special interest.

Refer to Section 7.3.5 Analysis of Submission-Specific Safety Issues “Psoriasis-Related Events” for further discussion regarding psoriasis adverse events.

Reviewer comment: The AEs leading to discontinuation reported in Phase 3 trials do not reveal any new safety concerns with the use of certolizumab in the psoriasis population.

Significant Adverse Events

Refer to Section 7.3.5 Analysis of Submission-Specific Safety Issues.

Treatment Emergent Adverse Events and Adverse Reactions

In the Phase 3 placebo-controlled period, treatment-emergent adverse events (TEAE) occurred in 63.5% of certolizumab 400mg subjects, 56.3% of certolizumab 200mg subjects, and 61.8% of placebo subjects. The most common TEAE were in the system/organ class (SOC) of Infections and Infestations, and included upper respiratory tract infections (URTI) and herpes infections. Because AEs of URTI, injection site reactions (ISR), herpes infection, gastroenteritis, skin infection, tinea infection, headache, and depression were reported under multiple preferred terms, we pooled these AEs to better evaluate their overall frequency of occurrence (see discussion and adverse reaction table below).

The AE category of upper respiratory tract infections (URTI) is comprised of pooled terms pharyngitis bacterial, pharyngitis streptococcal, upper respiratory tract infection bacterial, viral pharyngitis, viral sinusitis, nasopharyngitis, upper respiratory tract infection, and vial upper respiratory tract infection. The URTIs were the most commonly reported AE, occurring in 21.9% of subjects treated with certolizumab 400mg, 19.4% of

subjects treated with certolizumab 200mg, and 21% of subjects treated with placebo.

The AE category of injection site reaction (ISR) is comprised of pooled preferred terms injection site- reaction, pruritus, pain, erythema, swelling, bruising, and discoloration. A total of 25 events of ISR were reported by 18/692 (2.6%) subjects treated with certolizumab and 1/157 (0.6%) subject treated with placebo. The majority of reported ISR were mild or moderate in severity. One subject experienced a serious and severe ISR AE. All ISR events resolved. No ISR event resulted in discontinuation of treatment.

Refer to Section 7.3.5 Analysis of Submission-Specific Safety Issues for summary of subject who experienced serious and severe ISR AE.

After review of the safety database, we identified the TEAE occurring in 1% or more of subjects treated with certolizumab and more frequently than in the placebo group during the placebo-controlled period in Trials PS0005, PS0002, and PS0003. AEs of nasopharyngitis, upper respiratory tract infection, cough, pruritus, headache, occurred more frequently in subjects treated with certolizumab 400mg than certolizumab 200mg. The table below displays the TEAE.

Table 28: Treatment-Emergent Adverse Events Reported by >1% in One or More Certolizumab Groups in the Plaque Psoriasis Trials PS0005, PS0002, and PS0003

Adverse Events	Cimzia 400 n (%) N=342	Cimzia 200 n (%) N=350	Placebo n (%) N=157
Nasopharyngitis	33 (7.6)	28 (6.3)	22 (10.2)
Upper respiratory tract infection	20 (4.6)	15 (3.4)	9 (4.2)
Cough	11 (2.5)	5 (1.1)	3 (1.4)
Pruritus	11 (2.5)	4 (0.9)	9 (4.2)
Headache	10 (2.3)	5 (1.1)	3 (1.4)
Hypertension	8 (1.8)	10 (2.3)	5 (2.3)
Fatigue	7 (1.6)	4 (0.9)	3 (1.4)
Bronchitis	7 (1.6)	3 (0.7)	2 (0.9)
Rhinitis	7 (1.6)	2 (0.5)	0
Viral upper respiratory tract infection	6 (1.4)	6 (1.4)	1 (0.5)
Injection site reaction	6 (1.4)	4 (0.9)	0
Abdominal pain	5 (1.1)	2 (0.5)	0
Alopecia	5 (1.1)	1 (0.2)	0
Sinusitis	3 (0.7)	9 (2)	2 (0.9)
Pharyngitis	4 (0.9)	5 (1.1)	0

Source: Reviewer's own.

The table below displays adverse reactions recommended to be included in Section 6 of product labeling, along with terms pooled for each AR, where applicable.

Table 29: Adverse Reactions Occurring in ≥1% of Subjects in the CIMZIA Group and More Frequently than in the Placebo Group in the Plaque Psoriasis Trials PS0005, PS0002, and PS0003.

Adverse Reactions	Cimzia 400 n (%) N=342	Cimzia 200 n (%) N=350	Placebo n (%) N=157
Upper respiratory tract infections[1]	75 (21.9)	68 (19.4)	33 (21)
Headache[2]	13 (3.8)	10 (2.9)	4 (2.5)
Injection site reactions[3]	11 (3.2)	6 (1.7)	1 (0.6)
Cough	11 (3.2)	4 (1.1)	3 (1.9)
Herpes infections[4]	5 (1.5)	5 (1.4)	2 (1.3)

Source: Reviewer and Statistics' own.
[1]: Upper respiratory tract infection cluster includes upper respiratory tract infection, pharyngitis bacterial, pharyngitis streptococcal, upper respiratory tract infection bacterial, viral upper respiratory tract infection, viral pharyngitis, viral sinusitis, and nasopharyngitis.
[2]: Headache includes headache and tension headache.
[3]: Injection site reactions cluster includes injection site reaction, injection site erythema, injection site bruising, injection site discoloration, injection site pain, and injection site swelling.
[4]: Herpes infections cluster includes oral herpes, herpes dermatitis, herpes zoster, and herpes simplex.

Laboratory Findings

During the development program for certolizumab, evaluation of systemic safety included assessment of clinical laboratory data, which included hematology, serum chemistry, and urinalysis. Investigators performed clinical laboratory testing during Phase 2/3 trials per the schedule discussed in section 7.3.3 of this review.

We compared markedly abnormal laboratory values (Grade 3 or 4) reported during the placebo-controlled period and the all certolizumab treatment group, based on the Rheumatology Common Toxicity Criteria grading scale. Results of analyses of changes in hematology, clinical chemistry, and lipid values from baseline to post-baseline values during the placebo-controlled period and the all certolizumab treatment group were not considered to be clinically meaningful. No markedly abnormal laboratory values were reported at Baseline and few were reported during any visit during the placebo-controlled period. We observed no clinically relevant drug-related trends in abnormal laboratory values during the Phase 3 trials. Additionally, there were no clinically meaningful changes in laboratory values during the Safety Update reporting period.

One AE related to chemistry laboratory results was a SAE (transaminases increased, Subject PS0002 (b) (6)). See Section 7.3.4 Safety Results "Serious Adverse Events" for the discussion of this subject.

For discussion on hepatic laboratory values, see Section 7.3.5 Analysis of Submission-Specific Safety Issues "Hepatic Adverse Events."

The table below summarizes the markedly abnormal hematology laboratory values reported in Phase 3 trials.

Table 30: Phase 3 Trials: Summary of Markedly Abnormal Hematology Parameters during the Placebo-Controlled Period

Hematology Parameter	Cert 400mg	Cert 200mg	Placebo	Grade
Platelets	1/330 (0.3)	0	0	3: 1; 4: 0
Hemoglobin	4/339 (1.2)	1/347 (0.3)	1/155 (0.6)	3: 5; 4: 3
Lymphocytes	0	2/347 (0.6)	0	3: 0; 4: 2
Neutrophils	1/339 (0.3)	0	0	3: 1; 4: 0

Source: Reviewer's own and modified ISS Summary of Listings, Listing 2.1.1.
[1]: Rheumatology Common Toxicity Criteria Grade 3 or 4

Reviewer's comment: During the placebo-controlled period, 2 subjects treated with certolizumab 200mg reported Grade 3 decreases in hemoglobin and 2 subjects treated with certolizumab 400mg reported Grade 3 decreases in hemoglobin. Three of the 4 subjects treated with certolizumab reported Grade 3 decreases at Week 16 (end of placebo-controlled period) and the fourth subject had a subsequent increase in hemoglobin value. One subject treated with certolizumab 400mg reported 3 consecutive markedly abnormal decreases in hemoglobin; the first and second were Grade 4 and the third Grade 3. In the Safety Update Report, in subjects treated with certolizumab during Phase 2/3 trials, the majority of subjects with reported markedly abnormal hematology values had subsequent improvement in the hematology values.

Vital Signs

As discussed in section 7.3.3 of this review, vital signs were assessed at clinic visits during the Phase 2/3 trials and included measurement of weight, resting pulse rate, and blood pressure. Vitals signs were summarized and compared across common time points in the Phase 2/3 trials.

We compared markedly abnormal vital sign values (Grade 3 or 4) reported during the placebo-controlled period and the all certolizumab treatment group, based on the Rheumatology Common Toxicity Criteria grading scale. Results of analyses of changes in weight, systolic blood pressure, and diastolic blood pressure from baseline to post-baseline values during the placebo-controlled period and the all certolizumab treatment group were not considered to be clinically meaningful. During the placebo-controlled period, there were few shifts from not markedly abnormal at baseline to markedly abnormal at any post-baseline. We observed no clinically relevant drug-related trends in abnormal vital sign values during the Phase 3 trials. Additionally, there were no clinically

meaningful changes in vital sign values during the Safety Update reporting period.

Electrocardiograms (ECGs)

No ECGs were done in the Phase 3 trials for the plaque psoriasis indication.

QT

A thorough QT study was not performed for certolizumab in the plaque psoriasis development program. The ICH E14 guideline regarding the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs does not specifically address QT assessments for biologic agents. Recent publications, however, indicate a consensus that, because of their large size and high target specificity, mAbs such as certolizumab have a very low likelihood for ion channel interactions and therefore thorough QT/QTc studies are not generally needed.

Immunogenicity

Because therapeutic proteins have the potential to elicit an immune response, the applicant used validated assays to assess the immunogenicity of certolizumab in human serum in Phase 3 trials in the development program for plaque psoriasis.

After 48 weeks of treatment, the incidence of treatment-emergent anti-drug antibodies (TE-ADA) to certolizumab in the Phase 3 trials PS0005, PS0002, and PS0003 was 19.2% (54/281) for subjects receiving certolizumab 200mg and 8.3% (22/265) for subjects receiving certolizumab 400mg. Among the subjects with TE-ADA, the incidence of neutralizing antibodies was 45% (27/60) for subjects receiving certolizumab. However, immunogenicity incidences may be underestimated due to low drug tolerance levels of the ADA and NAb assays.

Development of ADAs was associated with approximately 2-fold lower PASI75 response rate in ADA positive subjects compared to ADA negative subjects. For subjects who became ADA positive, the incidence of AEs was greater prior to the positive result (61.5%) compared to after the positive result (56.1%), and both rates for ADA positive subjects were lower than for subjects who were ADA negative throughout the study (74%).

Development of ADAs was not associated with increased adverse events.

Refer to Section 6.2.1 for further discussion on immunogenicity.

7.3.5. Analysis of Submission-Specific Safety Issues

The applicant analyzed the safety parameters with pre-specified adverse events of special interest (AESI) which were related to the proposed certolizumab mechanism of action (immunomodulation via cytokine blockade), class effects associated with other anti-cytokine antibody therapies, particularly TNF inhibitors, and the specific risks, and co-morbidities observed in the target population.

AESI included:

- opportunistic and serious infection
- malignancy
- congestive heart failure and major adverse cardiovascular event
- demyelinating-like disorders
- hematopoietic cytopenic adverse event
- serious bleeding adverse event
- lupus and lupus-like disorders
- serious skin reactions

Additional analyses were conducted for depression-related events, hepatic adverse events, hypersensitivity reactions and anaphylactic events, injection site reactions, and psoriasis events.

Serious and Opportunistic Infections

The Phase 3 studies excluded subjects with a history of chronic or recurrent infections (more than 3 episodes requiring antibiotics or antivirals in the preceding year), recent serious or life-threatening infection within 6 months prior to Baseline, hospitalization for any infection in the last 6 months, and any current sign or symptoms that may indicate infection. Subjects with acute or chronic hepatitis B, hepatitis C, and HIV infection, as well as a history of active *Histoplasma*, *Coccidioides*, *Paracoccidioides*, *Pneumocystis*, nontuberculous mycobacteria, *Blastomyces*, or *Aspergillus* infection were also excluded.

The applicant utilized a two-stage approach to identify opportunistic infections:

- programmatic identification of serious and non-serious AEs that are always considered to be opportunistic infections based on a list of PTs identified by the study physician
- manual review of “case-by-case” PTs identified by the study physician that are confirmed or not confirmed to be opportunistic infections on a subject-by-subject basis.

The exposure-adjusted incidence rates (EAIR) of serious infections, including opportunistic infections, was greater for the certolizumab 400mg group (1.68/100 subj yrs) compared to the certolizumab (0.99/100 subj yrs). Twenty-four serious infections reported in 19 subjects occurred in subjects exposed to certolizumab (15 events in 11 subjects, 1.6%, in the certolizumab 400mg group and 9 events in 8 subjects, 1.1%, in the certolizumab 200mg group).

During the placebo-controlled period, 3 SAEs (abdominal abscess, hematoma infection, and pneumonia) were reported in the certolizumab 400mg group and 1 SAE (histoplasmosis) was reported in the certolizumab 200mg group. No subjects in the placebo group experienced a serious infection during the placebo-controlled period.

In the all certolizumab exposed groups, serious infections reported included disseminated tuberculosis, Bartholin's abscess, anal abscess, infected bite, cellulitis, urinary tract infection, appendicitis, ovarian abscess, pneumonia, klebsiella pneumonia, and bronchitis.

Seven subjects among 849 certolizumab-treated subjects reported an adverse event of tuberculosis (TB) (disseminated TB: 1, latent TB: 4, TB: 2). See narrative below for summary of the case of disseminated tuberculosis.

Selected Narratives of Serious and Opportunistic Infections

Histoplasmosis: A 29 –year-old White woman (Subject PS0003: (b) (6)) with a history of herpes simplex and pulmonary mass experienced an event of histoplasmosis prior to randomization and study drug administration based on an 8mm nodule in the lingula identified on screening chest X-ray with negative mycelial Ab and positive yeast Ab (titer 1:8). Computed tomography of the chest identified a calcified granuloma. Prophylactic treatment was initiated based on infectious disease consultation (could not rule out active infection). One dose of study drug administered. Repeat histoplasmosis serology unchanged and study drug withdrawn due to histoplasmosis (severe, not related). Subject discontinued study after receiving single dose of certolizumab 400mg.

Disseminated tuberculosis: A 46-year-old Algerian man (C87040: (b) (6)) with a history of previous methotrexate and cyclosporine treatment; possible previous etanercept treatment; and bilateral enlarged axillary and inguinal lymph nodes, had negative PPD and chest X-ray at screening and was randomized to certolizumab 400mg. Approximately 61-days after his first study drug dose, he was hospitalized for fever, diarrhea, asthenia and weight loss of 7kg. Chest X-ray showed bilateral miliary pattern suggestive of TB and CT of the abdomen showed liver hypertrophy. Liver biopsy confirmed diagnosis of TB. After starting anti-TB treatment, subject developed macrophage activation syndrome requiring intubation and ICU admission. The event of disseminated tuberculosis was considered an SAE (severe, highly probably related) and discontinued from the study. He was eventually discharged and reported to have good clinical and radiologic resolution of his TB 9 months after his initial hospitalization.

Reviewer comment: Serious infections, including opportunistic infections, are a known risk with CIMZIA and reflected in labeling, including a Box Warning. No new safety signals were identified in the psoriasis population.

Malignancy

The Phase 3 trials excluded subjects with a history of a lymphoproliferative disorder, including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease, and active malignancy or a history of malignancy except:

- less than 3 excised or ablated basal cell carcinomas of the skin
- 1 squamous cell carcinoma (SCC) (stage T1 maximum) excited or ablated within 2 years prior to screening
- SCC in situ excised or ablated within 6 months prior to screening
- uterine cervical carcinoma in situ successfully treated within 5 years to screening.

The table below summarizes the malignancies reported during Phase 2 and 3 trials. One subject (PS0002: (b) (6)) experienced an AE of basal cell carcinoma during the placebo-controlled period.

Table 31: Summary of Certolizumab-Treated Subjects with Malignancy in Phase 2 and 3 Trials

Study: Subject	Gender/Age/Race	Preferred Term	SAE
Non-melanoma Skin Cancers			
PS0005: (b) (6)	Male/68/White	basal cell carcinoma	Yes
PS0002: (b) (6)	Female/49/White	basal cell carcinoma	No
PS0002: (b) (6)	Male/52/White	basal cell carcinoma	Yes
PS0003: (b) (6)	Female/60/White	basal cell carcinoma	No
PS0003: (b) (6)	Female/64/White	keratoacanthoma	No
Other Malignancies			
PS0005: (b) (6)	Female/59/	adenocarcinoma of colon	Yes
PS0002: (b) (6)	Male/60/White	prostate cancer	Yes
PS0002: (b) (6)	Male/69/White	prostate cancer	not stated
PS0003: (b) (6)	Female/66/White	clear cell renal cell carcinoma	Yes
PS0003: (b) (6)	Male/29/White	anaplastic oligodendroglioma	Yes
		glioblastoma	Yes
PS0003: (b) (6)	Male/29/White	neoplasm malignant[1]	Yes
		Hodgkin's lymphoma[1]	Yes
PS0003: (b) (6)	Female/62/White	laryngeal cancer	Yes

Source: Modified from Safety Update Report, Table 2-7, ISS and SUR narratives and listings.
[1]: Same event: initially coded as "neoplasm malignant" and modified to "Hodgkin's lymphoma"

The results of population based, observational studies support the conclusion that patients with psoriasis are at increased overall risk of cancer.[24] The EAIR for any malignancy during the Phase 3 trials was 0.71/100 subj yrs and 0.5/100 subj yrs for any malignancy excluding non-melanoma skin cancers. The number of malignancies (excluding NMSC) from Phase 3 trials in the certolizumab groups is similar to the EAIR reported in moderate to severe psoriasis subjects in global trials of another TNF

[24] Brauchli YB, Jick SS, Miret M, Meier CR. Psoriasis and risk of incident cancer: an inception cohort study with a nested case-control analysis. J Invest Dermatol. 2009;129(11):2604–2612.

inhibitor, adalimumab (0.6/100 patient yrs).[25]

Reviewer comment: Malignancy is a known risk with CIMZIA and reflected in labeling, including a Box Warning. No new safety signals were identified in the psoriasis population.

Major Adverse Cardiovascular Events
The Phase 3 trials excluded subjects with congestive heart failure (CHF) and severe, progressive, or uncontrolled cardiac disease.

The UCB-defined search criteria for identifying serious cardiovascular events included:

- All serious TEAEs which code to a PT included in the search=Broad scope of the following standardized MedDRA queries (SMQ):
  - Hemorrhagic central nervous system vascular conditions (SMQ)
  - Ischemic central nervous system vascular conditions (SMQ)
  - All serious TEAEs which code to a PT included in the HLT "ischemic coronary artery disorders"
  - All serious TEAEs, which code to a PT included in any of the following HLTs: heart failures NEC, left ventricular failures, or right ventricular failures, and which also code to the SOC of "Cardiac Disorders" as the primary SOC.

In view of the epidemiologic associations between psoriasis and cardiovascular (CV) comorbidities, and the potential association between anti-cytokine therapies used in the treatment of moderate to severe psoriasis and CV events, the applicant conducted analyses on all events related to the CV system.

During the placebo-controlled period of Phase 2 and 3 trials, no adverse event of CHF was reported, while 1 subject experienced a MACE of acute coronary syndrome (certolizumab 400mg group). In the all certolizumab treated group in Phase 2 and 3 trials, 1 additional subject reported CHF and 4 subjects reported MACE of CVA, TIA (2), and extradural hematoma. Although subjects were all receiving study drug when the CHF events and MACE occurred, all subjects had cardiac risk factors, except for the subject who experienced extradural hematoma after a traffic accident (not related).

The table below summarizes the CHF events and MACE reported in the Phase 2 and 3 trials.

[25] Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, and Lacerda APM. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis.2013; 72(4): 517-524.

Table 32: Summary of Certolizumab-Treated Subjects with CHF Events or MACE in Phase 2 and 3 Trials

Study: Subj ID	Treatment (initial/maint)	Cardiac Risk Factors	Adverse Event	Event Day	Outcome
PS0005: (b) (6)	placebo/ cert 200mg Q2W	impaired fasting glucose, HTN, hyperlipidemia, smoker	CVA	D317	Resolved
PS0002: (b) (6)	cert 400mg Q2W/ cert 400mg Q2W	history of MI and CVA, HTN, hyperlipidemia, congenital cardiac murmur, ECG prolonged QT	CHF	D204	Resolving at time of database lock
PS0002: (b) (6)	placebo/ cert 400mg Q2W	smoker, type 2 DM	TIA	D718	Not resolved at database lock
PS0002: (b) (6)	cert 200mg Q2W/ cert 200mg Q2W	DM, HTN	TIA	D248	Resolved
PS0003: (b) (6)	etn 50mg/ cert 400mg	none	extradural hematoma	D380	Resolved.
PS0003: (b) (6)	cert 400mg Q2W/ cert 200mg Q2W	HTN, BMI 40.3	ACS	D91	Resolved
PS0003: (b) (6)	placebo/ cert 400mg Q2W	HTN, hyperlipidemia	CHF exacerbation	D224	Resolved

Source: ISS Listing 1.2.6.4, Safety Update Report Listing 1.2.6.4, and ISS and SUR narratives and listings.
maint: maintenance, D: Day, etn: etanercept, MI: myocardial infarction, CVA: cerebrovascular accident, HTN: hypertension, ACS: acute coronary syndrome, TIA: transient ischemic attack, DM: diabetes mellitus

Reviewer comment: CHF is a known risk with CIMZIA and reflected in labeling. No new safety signals were identified in the psoriasis population.

Demyelinating-like Disorders

The Phase 3 trials excluded subjects with a history of or suspect of having demyelinating diseases of the central nervous system or with severe, progressive, or uncontrolled neurological disease.

No subjects reported demyelinating disorders during the placebo-controlled period of the Phase 2 and 3 trials. In the all certolizumab treated group, 2 subjects experienced demyelinating disorders. The narratives are included below.

Narratives of Demyelinating Disorders

Multiple sclerosis (MS): a 39-year-old White man (PS0002: (b) (6)) with a history of adalimumab use, experienced an SAE of multiple sclerosis 348 days after his first dose of study drug. Study drug was discontinued and the event was considered related to study drug.

Primary progressive MS: a 53-year-old White man (PS0003: (b) (6)) with a history of secukinumab use and a 2-year history of gait disturbance and falls was diagnosed with

primary progressive MS based on neurology consultation and MRI. Study drug was discontinued and the event was not considered related to study drug.

Reviewer comment: I agree with the investigator that subject PS0003: (b) (6) 's AE was likely unrelated to certolizumab given the chronicity of symptoms prior to trial participation. For subject PS0003: (b) (6), the onset of disease 348 days after starting certolizumab. Demyelinating disease is a known risk with CIMZIA and reflected in labeling. No new safety signals were identified in the psoriasis population.

Hematopoietic Cytopenic Adverse Events
The Phase 3 trials excluded subjects with clinically significant laboratory abnormalities (e.g., $<3.0x10^9$/L) and subjects with a current or recent history, as determined by the Investigator, of severe, progressive, and/or uncontrolled hematological disease

No cytopenic adverse events were reported during the placebo-controlled period for Phase 2 and 3 trials. One subject in the all certolizumab exposed group experienced a cytopenic AE of abnormal blood count (see narrative below).

Narrative of Cytopenic Adverse Event
Abnormal blood count: A 66-year-old White man (PS0002: (b) (6)) randomized to placebo experienced an AE of abnormal blood count during the placebo-controlled period approximately 6 days after his only dose of study drug (certolizumab 200mg). He was hospitalized for evaluation and noted to have anemia and low magnesium. He was discharged after 1 day with magnesium supplements and subsequent hemoglobin level was normal. He was discontinued from the study due to the event. He died 191 days after his only dose of certolizumab, 171 days after study withdrawal. Cause of death is unknown, and the investigator considered the death unrelated to study drug.

Reviewer comment: I agree with the investigator that given the long duration between the abnormal blood count and death that the death is unlikely related to study drug. The occurrence of an abnormal blood count may be related to study drug. Cytopenia and pancytopenia are known risks with CIMZIA and reflected in labeling. No new safety signals were identified in the psoriasis population.

Serious Bleeding Adverse Events
The Phase 3 trials excluded subjects with a current or recent history, as determined by the Investigator, of severe, progressive, and/or uncontrolled hematological disease.

During the placebo-controlled period of Phase 2 and 3 trials, 1 subject in the certolizumab 400mg group (hematoma infection and contusion, same subject) and 2 subjects in the certolizumab 200mg group (splenic hematoma and hemothorax, 1 subject each) were reported. In the all certolizumab exposed group, 11 subjects experienced 14 serious bleeding AEs. The table below summarizes the serious bleeding events reported in the Phase 2 and 3 trials.

Table 33: Summary of Certolizumab-Treated Subjects with Serious Bleeding Adverse Events in Phase 2 and 3 Trials

Study: Subject	Gender/Age/Race	Preferred Term	Related
C87040: (b) (6)	Male/30/White	contusion[1]	Unlikely
PS0005: (b) (6)	Male/51/White	splenic hematoma[2]	No
		hemothorax[2]	No
PS0002: (b) (6)	Female/54/White	rectal hemorrhage	No
PS0002: (b) (6)	Female/31/White	Menorrhagia	No
PS0002: (b) (6)	Female/38	DIC	Not stated
		hemorrhagic necrotic pancreatitis	Not stated
PS0002: (b) (6)	Female/63	genital hemorrhage	No
PS0002: (b) (6)	Male/64/White	hematoma infection[1]	No
		contusion[1]	No
PS0002: (b) (6)	Male/59/White	epistaxis	No
PS0003: (b) (6)	Female/22/White	extradural hematoma[1]	No
PS0003: (b) (6)	Female/34/White	hemorrhoidal hemorrhage	No
PS0003: (b) (6)	Male/51/White	urinary bladder hemorrhage	No

Source: Modified Safety Update Report, Table 2-8; and ISS and SUR narratives and listings.
DIC: disseminated intravascular coagulation
[1]: secondary to traffic accident, resolved
[2]: secondary to fall

Narrative of Serious Bleeding Adverse Event

DIC, hemorrhagic necrotic pancreatitis: A 40-year-old woman (PS0002: (b) (6)) with a history of hepatic steatosis and morbid obesity developed a bacterial infection 586 days after starting certolizumab 400mg Q2W. Subsequent laboratory results showed an increasing white count and progressively increasing liver enzymes and total bilirubin. The subject was admitted to the hospital approximately 9 weeks after the bacterial infection for severe jaundice and elevated liver enzymes and total bilirubin. She died the day after admission and autopsy concluded death due to cardiac arrest secondary to rapidly progressive multifunctional liver failure and hypovolemic shock secondary to hemorrhagic pancreatic necrosis.

Reviewer comment: Four of the 11 subjects (5 of 14 events) were due to trauma and in 10/11 subjects (1 not stated in narrative) the AE was considered not related to study drug. Serious bleeding that may occur due to cytopenia and pancytopenia are known risks with CIMZIA and reflected in labeling. No new safety signals were identified in the psoriasis population.

Lupus and Lupus-like Disorders

The Phase 2 and 3 studies excluded subjects with systemic lupus. No AE of lupus or lupus-like disorder were reported during the Phase 2 and 3 studies.

Serious Skin Reactions

No AE of serious skin reaction were reported during the Phase 2 and 3 studies.

Depression-Related Events

Depression is known co-morbidity in patients with plaque psoriasis. Biologic

development programs for treatment of plaque psoriasis typically monitor for depression-related AEs.

During the placebo-controlled period, 6 subjects (1.4%) in the certolizumab 400mg group, 4 subjects (0.9%) in the certolizumab 200mg group, and 4 subjects (1.9%) of the placebo group reported an AE of depression. Of these, 1 subject in the certolizumab 200mg group reported an SAE of depression (see narrative below).

No additional depression-related events were noted in the Safety Update Report.

Narrative of Depression-Related Events
SAE depression/suicide attempt: A 59-year-old White man (PS0002: (b) (6)) with a history of depression and insomnia, experienced a non-SAE of depression during the placebo-blinded period that was considered mild and not resolved. The subject reported further worsening of depression and suicide attempt approximately two months later that led to hospitalization and considered severe. The subject was discharged on Paxil and reported improved mood. Subsequently, the subject reported depressed mood 4-5 days post-injection that would improve 4-5 days prior the next injection. The subject withdrew from the study and requested the investigator and applicant not to access his psychiatric records.

Reviewer comment: Subject PS0002: (b) (6) reported the only event of suicide attempt and experienced the SAE related to depression. It appears that treatment with certolizumab may have contributed to worsening of depression and suicide attempt in this subject. Depression is a known morbidity in psoriasis patients. No new safety signals were noted in the psoriasis population. No labeling changes are recommended.

Hepatic Adverse Events
The Phase 3 trials excluded subjects with severe, progressive, or uncontrolled hepatic disease. Subjects with AST or ALT greater than 3x upper limit of normal (ULN) or total bilirubin >1.5ULN were also excluded.

Hepatic adverse event monitoring included the following 5 SMQs using the narrow search grouping: cholestasis and jaundice of hepatic origin; hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; hepatitis, non-infectious; liver-related investigations, signs, and symptoms; and liver-related coagulation and bleeding disturbances. Hy's law criterion was defined as bilirubin elevation ≥2 ULN, and ALT or AST elevation ≥3xULN at the same visit. Alkaline phosphatase testing was not conducted in the Phase 3 trials.

During the placebo-controlled period, 50 hepatic events were reported in 28 subjects (4%) treated with certolizumab (certolizumab 400mg: 4.9% and certolizumab 200mg: 3.2%) compared to 7 hepatic events reported in 6 subjects (3.8%) treated with placebo. Most events were mild or moderate, with 6 severe hepatic events in 3 subjects:

- 1 subject in certolizumab 400mg group: ALT increased, AST increased, and GGT increased

- 1 subject in certolizumab 200mg group: 1 subject with 2 events of transaminases increased
- 1 subject in placebo group: GGT increased

Two subjects discontinued due to hepatic events (see narratives below). One SAE of transaminases increased was reported in the certolizumab 200mg group (see narrative below). Seven subjects (2.1%) in the certolizumab 400mg group, 10 subjects (2.9%) in the certolizumab 200mg group, and 2 subjects (1.2%) in the placebo group reported markedly abnormal post-baseline elevations of either ALT or AST. One subject had ALT ≥10ULN in the certolizumab 200mg group (see narrative below). The elevations in bilirubin were similar for the certolizumab 400mg group, certolizumab 200mg group, and placebo group (bilirubin ≥1xULN: 8.8%, 6.6%, and 6.5%, respectively; bilirubin ≥1.5xULN: 1.5%, 2%, and 1.2%, respectively).

In the all certolizumab exposed group, the EAIR for hepatic adverse events was lower compared to EAIR for hepatic events reported in the placebo-controlled period (certolizumab 400mg: 9.3 versus 10.64 events/100 subj yrs; certolizumab 200mg: 8.17 versus 16.31 events/100 subj yrs). One subject experienced ALT elevation ≥20xULN and AST elevation ≥10xULN reported as severe AEs (see narrative below). Three additional SAEs were reported in the all certolizumab exposed group (certolizumab 400mg: cholecystitis; certolizumab 200mg: drug-induced liver injury and hepatitis) (see narratives below).

No subject in the placebo-controlled period group met Hy's Law criterion.

The Safety Update Report includes 2 additional hepatic SAEs. One SAE of hepatic failure resulted in death (see Section 7.3.4 Safety Review "Deaths" for discussion), and one SAE of drug-induced liver injury (see narrative below). The former subject is also the only subject who met Hy's Law criterion, likely due to non-drug etiologies.

Narratives of Hepatic Adverse Events in Placebo-Controlled Period

Transaminases increased: A 59-year-old White woman (PS0002: (b) (6)) with a history of diabetes, hepatic steatosis, and hypertension and elevated baseline values for AST, ALT, and GGT experienced increasing values at subsequent visits. Abdominal ultrasound and CT showed fatty liver and hepatomegaly. Study drug was withdrawn and subject discontinued.

AST increased, ALT increased, GGT increased: A 50-year-old White man (PS0003: (b) (6)) with a history of alcohol abuse and baseline elevated GGT experienced 4 AEs of increased AST and single events of increased ALT and increased GGT. Additionally, the subject reported non-serious AESI of thrombocytopenia, leukopenia, and neutropenia that led to study drug interruption. The AESI were reported to be resolved without sequelae. The study drug was withdrawn and subject was discontinued due to adverse events and alcohol abuse.

SAE, transaminases increased and ALT ≥10xULN: A 33-year-old White man (PS0002: (b) (6)) with a BMI of 39.1 kg/m^2 experienced increasing ALT, AST, GGT, and

LDH values. He was hospitalized Day 98 for evaluation of increased transaminases (ALT ≥10xULN, AST ≥5xULN, and underwent liver ultrasound revealing massive lipid infiltration. Study drug dosing was interrupted during the hospitalization with normal AST, ALT, GGT, and LDH at the Week 16 visit. Study drug was restarted with ALT, AST, and GGT values increased at Week 24. Study drug was withdrawn and subject discontinued from study for non-compliance. Subject was also taking dietary supplements. Additionally, the subject had an AE of hepatic steatosis.

Narratives of Hepatic Adverse Events in All Certolizumab Exposed Group
SAE hepatitis, and ALT elevation ≥20xULN and AST elevation ≥10xULN: A 30-year-old White man (PS0003: (b) (6)) with negative hepatitis B and C at screening experienced serious AE of hepatitis. The subject was hospitalized for non-serious AEs of elevated AST, ALT, and GGT. Study drug was interrupted. Liver ultrasound revealed enlarged liver with increased echogenicity. The subject was diagnosed with hepatitis during the hospitalization. Subject was discharged and restarted on study drug. The subject had subsequent mild elevations in AST, ALT, and GGT.

SAE cholecystitis: 43-year-old White woman with no relevant medical history was hospitalized for cholecystitis, confirmed by CT and MRI imaging. She underwent laparoscopic cholecystectomy and discharged the same day. Study drug was not discontinued or interrupted.

SAE drug-induced liver injury: A 75-year-old White woman (PS0002: (b) (6)) with a history of latent TB and hypercholesterolemia experienced SAE drug-induced liver injury (related) of severe intensity requiring hospitalization. She was diagnosed with psoriatic arthropathy during the admission. Abdominal ultrasound revealed steatosis of the liver. Study drug was withdrawn and the subject discontinued from the study.

Narratives of Hepatic Adverse Events from Safety Update Report
SAE drug-induced liver injury: A 62-year-old man (PS0002: (b) (6)) with a history of drug hypersensitivity, psoriatic arthropathy, hypertension, and "periodic abuse of alcohol" experienced yellowing of the skin and dark urine leading to hospital admission. Study drug was withdrawn on admission. Laboratory testing revealed pre-renal failure and elevated AST and bilirubin. Abdominal imaging revealed an enlarged liver and dilation of intrahepatic bile ducts. Endoscopic retrograde cholangiopancreatography was performed and cholecystolithiasis was diagnosed. The patient deteriorated. Further evaluation revealed hepatomegaly, renal failure, and chronic pancreatitis. Toxic liver disease with cholestasis was diagnosed with gradual improvement with intensive treatment. The subject was eventually discharged 20 days after admission. Subject was discontinued from the study shortly after discharge from hospital.

Hypersensitivity Reactions and Anaphylactic Events
The Phase 3 trials excluded subjects with a known hypersensitivity of excipients of certolizumab or with a history of adverse reaction to polyethylene glycol.

The applicant identified hypersensitivity reactions based on AEs reported the same day

or within one day after when a study medication injection reaction was reported, and include the preferred terms below:

- Administration site hypersensitivity
- Documented hypersensitivity to administered product
- Drug hypersensitivity
- Hypersensitivity
- Hypersensitivity vasculitis
- Infusion site hypersensitivity
- Injection site hypersensitivity
- Medical device site hypersensitivity
- Type II hypersensitivity
- Type IV hypersensitivity reaction

The applicant identified the anaphylaxis reaction using the MedDRA SMQ algorithmic approach search for identifying AEs reported on the same day or within one day of study drug administration and fulfill any of the following 3 criteria:

- If a subject reports any AE which codes to a PT included in Category A, then the event will be flagged as an anaphylactic reaction and summarized as such in the table.
- If a subject reports any AE which codes to a PT included in Category B AND reports any AE which codes to a PT included in Category C, and both AEs have the same start date, then both events will be flagged as anaphylactic reactions and summarized as such in the table.
- If a subject reports any AE which codes to a PT included in Category D AND reports (either a AE which codes to a PT included in Category B OR a AE which codes to a PT included in Category C), and both AEs have the same start date, then both events will be flagged as anaphylactic reactions and summarized as such in the table.

During the placebo-controlled period, one subject experienced an SAE of anaphylactic reaction (anaphylactoid reaction) that led to study drug withdrawal and subject study discontinuation. See narrative summary below.

In the Safety Update Report, one hypersensitivity reaction of “worsening of early bloomer allergy” was reported in a subject (PS0005: (b) (6)) with a history of allergy to plants. This event did not lead to study drug discontinuation. The AE was reported to be mild in intensity and resolving.

Narratives of Hypersensitivity Reactions and Anaphylactic Events

Anaphylactoid reaction: A 44-year-old man (PS0005: (b) (6)) experienced uvula swelling after leaving the study site. Additional symptoms included dizziness, hot flushes, pulmonary burning sensation, dyspnea, throat swelling, and redness. Anaphylactoid reaction was diagnosed and treated with adrenaline, decadron, Benadryl, and dimenhydrinate. The patient was discharged from the hospital the same day. The

event was considered severe and related to study medication. Study drug withdrawal and subject discontinued from the study.

Reviewer comment: The verbatim term of "worsening of early bloomer allergy" was translated to the preferred term "hypersensitivity." With a history of allergy to plants, this event is more likely a seasonal pollen allergy and less likely a true hypersensitivity reaction.

Reviewer comment: Labeling includes hypersensitivity reactions in Section 5.4, reproduced below.

> **5.4 Hypersensitivity Reactions**
> The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, anaphylactoid reaction, dyspnea, hypotension, rash, serum sickness, and urticaria. Some of these reactions occurred after the first administration of CIMZIA. 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)]*.

We recommend the updating the Highlights and Section 4 Contraindications to include:

> **Highlights - Contraindications**
> Serious hypersensitivity reaction to certolizumab pegol or to any of the excipients.
>
> **4 Contraindications**
> CIMZIA is contraindicated in patients with a previous serious hypersensitivity reaction to certolizumab pegol or to any of the excipients [see Warnings and Precautions (5.4)].

Injection Site Reactions
The applicant identified injection site reactions using the MedDRA HLT "injection site reactions."

During the placebo-controlled period, a dose-response was noted for injection site reactions with 3.5% of subjects in the certolizumab 400mg group reported 7 events, 1.7% of subjects in the certolizumab 200mg group reported 18 events, and 0.6% of subjects in the placebo group reported 1 event. One event (injection site reaction) was considered severe and a SAE (see narrative below). No injection site reaction led to withdrawal of study drug.

The Safety Update Report included 42 injection site reactions in 29 subjects, with a profile similar to the initial filing.

Narratives of Injection Site Reactions
SAE injection site reaction: A 50-year-old White man experienced severe pain and

developed a hematoma at the injection site (left abdomen) that expanded up to 20cm. The subject did not have problems with previous injections. Two hours after the injection, he developed fever, chills, rigors, myalgia, and arthralgia and was hospitalized for sepsis evaluation. Lumbar puncture was done and antibiotics started. Blood cultures, cerebral spinal fluid analysis, chest X-ray, and urine cultures were negative. The subject was discharged. The subject did not have any reactions with subsequent injections. Study drug was reported as "dose not changed."

Reviewer comment: Injection site reactions will be included in Section 6.1 Clinical Trials Experience in Table 2 "Adverse Reactions Occurring in ≥1% of Subjects in the CIMZIA Group and More Frequently than in the Placebo Group in the Plaque Psoriasis Studies 1, 2, and 3."

Psoriasis Adverse Events

The Phase 2 and 3 studies excluded subjects with erythrodermic, guttate, palmoplantar or generalized pustular forms of psoriasis. New or worsening psoriasis is a reported effect of TNF inhibitors for other indications.

In the placebo-controlled period, 1.8% of subjects in the certolizumab 400mg group, 1.1% of subjects in the certolizumab 200mg group, and 4.5% of subjects in the placebo-group experienced an HLT event of psoriatic condition. No events of guttate, erythrodermic, or pustular psoriasis were reported during the placebo-controlled period. No event was considered a SAE or led to study discontinuation.

Reviewer comment: During the placebo-controlled period, the increased occurrence in the placebo group for psoriatic conditions is expected, as these subjects did not receive treatment for their disease. Regarding the AEs of erythrodermic and guttate psoriasis, only single events were reported up to the Safety Update Report cut date, and thus numbers are too few to recommend any change to labeling.

In the all certolizumab exposed group, 1 subject experienced an event of erythrodermic psoriasis (SAE, severe, not related) that led to study discontinuation and 1 subject experienced an event of guttate psoriasis (mild, non-SAE, resolving). One subject experienced an AE of psoriasis that was considered severe, not related) that led to study discontinuation.

The Safety Update Report included 61 events in the HLT of psoriatic conditions in 49 subjects and reported a total of 3 subjects experiencing guttate psoriasis, 1 subject experiencing erythrodermic psoriasis, and 2 subjects experiencing pustular psoriasis during the Phase 3 trials.

Reviewer comment: psoriasis-related adverse reactions are known risks of TNF inhibitors. Section 6.2 of the CIMZIA Prescribing Information includes:

> *Skin*: case of severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and new or worsening psoriasis (all

sub-types including pustular and palmoplantar) have been identified during post-approval use of TNF blockers.

We recommend inclusion of psoriasis-related adverse reactions in Section 6.1 to include guttate, erythrodermic, and pustular psoriasis.

7.3.6. Safety Analyses by Demographic Subgroups

The review team conducted analyses to evaluate the safety profile of certolizumab in different populations. The results indicated that there were no substantial differences in the risk of adverse reactions in demographic subgroups. However, because the trials were not powered for these analyses, the data must be interpreted with caution. A slightly greater proportion of female subjects who received either certolizumab or placebo reported adverse reactions of anemia, palpitations, vertigo, diarrhea, nausea, vomiting, injection site reaction, upper respiratory tract infection, oral herpes, depression, anxiety, and pruritus than in male subjects. A greater proportion of male subjects who received either certolizumab or placebo reported adverse events of hypothyroidism and diabetes mellitus than in female subjects. Approximately 92.7% of subjects enrolled in the Phase 3 trials were adults ≤ 64 years of age; therefore, because of the limited number of subjects age >65 years, it would be difficult to detect any differences in safety compared with younger subjects. The data for safety by race is difficult to interpret due to the relatively small sample sizes of the non-White subgroups (White 94.4%; Asian 1.9%; American Indian or Alaska native 0.2%; Black or African American 2.2%, and other/mixed 1.2%).

7.3.7. Supportive Safety Data from Other Clinical Trials

The applicant submitted supportive data from two Phase 2 trials (C87040 and C87044). A brief description of the study designs and results are provided below.

Trial C87040

"Multicentre, dose response, randomized, double blind, parallel, 3 arms, placebo-controlled clinical trial to evaluate the efficacy and the safety of subcutaneous CDP870 (certolizumab) at 2 different 12 weeks dose regimens (400mg initial dose at week 0 with 200mg every 2 weeks thereafter and 400mg every 2 weeks), followed by a minimum of 12 weeks of follow-up without treatment (or until relapse) in subjects suffering from moderate to severe chronic plaque psoriasis who are candidates for systemic therapy and/or phototherapy and/or photochemotherapy."

This was a two-part, randomized, placebo-controlled, double-blind, multi-center trial of certolizumab (400mg loading dose followed by 200mg Q2W and 400mg Q2W, for 12 weeks of treatment) in adult subjects with chronic, moderate to severe plaque psoriasis who were candidates for systemic therapy or phototherapy.

Safety Results

There were no deaths during Trial C87040, while 2.9% (certolizumab 400mg: 5, certolizumab 200mg: 2, and placebo: 2) of subjects experienced SAEs. One subject experienced a SAE of arteriosclerosis of coronary artery soon after screening and was not included in the trial. One subject in the placebo group experienced a SAE of diarrhea hemorrhagic and treatment was discontinued. In the certolizumab 200mg group, one subject experienced a SAE of contusion and one subject experienced SAEs of urinary tract infection and gastroenteritis. In the certolizumab 400mg group, two subjects experienced SAEs of pregnancy (one subject had two events; subject with single event discontinued), one subject experienced disseminated tuberculosis (discontinued after receiving all treatment injections), one subject experienced anxiety (2 events) and gastroenteritis, and one subject experienced a SAE of psoriasis (discontinued).

A total of 124 subjects (70.9%) experienced AEs. The most frequently reported AEs were nasopharyngitis (certolizumab 400mg: 21.1%, certolizumab 200mg: 16.7%, and placebo: 14%) and headache (certolizumab 400mg: 21.1%, certolizumab 200mg: 21.7%, and placebo: 15.5%). Twenty-eight subjects discontinued treatment due to AE (certolizumab 400mg: 3, certolizumab 200mg: 2, and placebo: 3). Most AEs experienced were mild or moderate in severity. Severe AEs were experienced by 7% of certolizumab 400mg subjects, 6.7% of certolizumab 200mg subjects, and 12.1% of placebo subjects.

There were no clinically meaningful changes in laboratory values, vital signs, or ECG parameters.

Study C87044

"Follow-up of Study C87040: Multicentre, double-blind study to describe the efficacy and safety of re-treatment with CDP870 (certolizumab) subcutaneous at 2 different dose regimens (400mg initial dose at Week 0 with 200mg every 2 weeks thereafter and 400mg every 2 weeks) or placebo for 12 weeks, in subjects suffering from moderate to severe chronic plaque psoriasis who are candidates for systemic therapy and/or phototherapy and/or photochemotherapy, having responded to treatment in Study C87040 and having subsequently relapsed."

This was an extension study of Trial C87040 that included subjects who completed and responded (PASI75 compared to baseline) to treatment after 12 weeks of treatment who then relapsed during the 24-week follow-up period after stopping study treatment. Subjects who were randomized to certolizumab 400mg followed by 200mg Q2W received the same dosing regimen in Trial C87044. Subjects who were randomized to certolizumab 200mg Q2W restarted the same dosing regimen in Trial C87044.

Safety Results

There were no deaths during Trial C87044, but one death occurred after the trial (cerebral hemorrhage 18 weeks after last study injection). One subject failed screening after experiencing a SAE of suspected tuberculosis based on positive PPD, and one subject experienced a SAE of melanocytic nevus (became darker) that was revised to

benign lentigo simplex after excision. No subjects discontinued study treatment due to AE.

Fewer AEs were experienced by subjects in Trial C87044 compared to Trial C87040 (45.1% vs 66.2%). As in Trial C87040, nasopharyngitis (11.3%) and headache (5.6%) were the most common AEs reported, but they occurred at lower rates compared to Trial C87044.

There were no clinically meaningful changes in laboratory values, or vital signs, or ECG parameters compared to Trial C87040.

7.3.8. Additional Safety Explorations

Safety Update Report

No new safety signals were identified in the Safety Update (SDN 1631 dated 11/17/2017). The applicant submitted safety data for Phase 3 Trials PS0005, PS0002, and PS0003. The focus of this submission was the subject study drug exposure and the following key safety events, which occurred in subjects receiving certolizumab: deaths, SAEs, AESI, AEs resulting in discontinuation of study agent, anti-CZP antibodies, clinical laboratory values, and vital signs. Discussion of any events included in the Safety Update Report are included in the respective section throughout the Section 7.3 Review of Safety.

Weight-Based Analysis

The Agency requested additional analyses based on weight group for efficacy, safety, and immunogenicity. The findings were included into the overall assessment of safety.

Human Reproduction and Pregnancy

Requirements for females of childbearing potential who were enrolled in certolizumab development program included the use of effective forms of contraception; negative serum pregnancy tests at screening; and urine and serum pregnancy testing at Baseline, Week 48, Week 144/Completion, and Follow-Up Visit 10 weeks after last dose. Subjects who became pregnant withdrew from treatment and, if feasible, were followed until delivery and 30 days after delivery. Pregnancy outcomes such as miscarriage, spontaneous or elective abortion, unintended pregnancy after hormonal failure (if used correctly), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of a baby were reported as SAEs.

Among subjects receiving certolizumab in the development program through the safety cut date of August 29, 2017, there were 9 pregnancies in 8 subjects. See Section 7.3.4 Review of Safety “Serious Adverse Events” for summary table of pregnancies in subjects treated with certolizumab.

Section 8.1 and 8.2 of the CIMZIA Prescribing Information includes information on pregnancy and lactation, including pregnancy exposure registry contact information. Section 8 of the label was already in accordance with the Pregnancy and Lactation Labeling Rule and no changes are recommended.

We recommend registries to evaluate pregnancy outcomes in a cohort of women exposed to certolizumab compared to an unexposed control population. Refer to Section 12 Postmarketing Requirements and Commitments.

Human Carcinogenicity or Tumor Development

As large proteins, monoclonal antibodies are not expected to gain access to the nucleus and directly interact with DNA to promote carcinogenesis. Certolizumab will be catabolized to peptides and constituent amino acids via normal metabolic pathways. However, for any product that produces immunosuppression and which is indicated for chronic administration, there is a theoretical risk of increased malignancy. In patients with psoriasis, this risk may be potentiated by prior exposure to other immunosuppressive agents or other therapies that may enhance tumor development such as phototherapy.

Nonclinical pharmacology/toxicology studies were submitted and reviewed under the original BLA. No safety issues were identified and additional nonclinical studies are not needed to support the new efficacy supplement.

Section 13.1 of the CIMZIA Prescribing Information states:

> 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.

Pediatrics and Assessment of Effects on Growth

The applicant has not conducted an evaluation of the safety and efficacy of certolizumab in the plaque psoriasis pediatric population, but pediatric studies are planned or ongoing in pediatric subjects with (b) (4) polyarticular-course juvenile idiopathic arthritis, and active Crohn's disease.

Section 8.4 of the CIMZIA Prescribing Information states:

> Safety and effectiveness in pediatric patients have not been established. Due to its inhibition of TNFα, CIMZIA administered during pregnancy could affect immune responses in the *in utero*-exposed newborn and infant *[see Use in Specific Populations (8.1)]*.

Because the product is proposed for a new indication, approval of certolizumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy triggers the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c). The applicant submitted an initial Pediatric Study Plan (iPSP) on June 11, 2014, prior to opening the IND on September 10, 2014 (b) (4)

The Division discussed the proposed iPSP with the Pediatric Review Committee (PeRC) on October 8, 2014. (b) (4)

The applicant submitted an amended iPSP (b) (4) on January 12, 2015. (b) (4)

The applicant submitted an agreed upon iPSP on January 20, 2015. The document reflects the revisions to the amended iPSP submitted on January 12, 2015. PeRC communicated their agreement with the agreed upon iPSP to DDDP on February 4, 2015.

Refer to Section 9 for the pediatric study requirement for certolizumab under PREA.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
In the development program, there were no AEs of overdose of certolizumab.

Section 10 of the CIMZIA Prescribing Information states:

> The maximum tolerated dose of certolizumab pegol has not been established. Doses of up to 800mg 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.

Drug Abuse Potential/ Withdrawal and Rebound

There is no data to support an association of monoclonal antibodies including certolizumab with the potential for addiction, abuse, withdrawal, or rebound. Therefore, the applicant did not evaluate abuse potential.

7.3.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The safety profile of CIMZIA has been monitored since its approval. This review did not reveal any new safety concerns since the last labeling update in March 20, 2018.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the certolizumab safety data identified no new safety signals. There are no safety concerns that are expected to change the favorable risk/benefit assessment or lead to increased risk with administration of certolizumab in the postmarket setting. However, additional data are needed to characterize the safety profile of the proposed product in special populations (pregnant and lactating females and the pediatric population age ≥ 6 years. Refer to Section 12 of this review for the postmarketing requirements and commitments.

7.3.10. Integrated Assessment of Safety

The safety profile for certolizumab was adequately characterized during the drug development program. The primary safety database consisted of subjects from the Phase 2 trials C87040 and C87044 and Phase 3 trials PS0005, PS0002, and PS0003, and included 1083 subjects treated with certolizumab at the proposed dose of 400mg SC. Of these 1083 subjects, 672 subjects were exposed for at least 12 months, 587 for 18 months, and 469 for 24 months.

One anaphylactic event (anaphylactoid reaction) occurred in subjects treated with certolizumab. Information regarding hypersensitivity reactions will be conveyed in Section 4 (Contraindications) and Section 5.4 (Warnings and Precautions) in product labeling.

Treatment with certolizumab did not appear to increase the risk of mortality. There were 6 deaths reported in the five Phase 2/3 trials in subjects receiving certolizumab. During

the placebo-controlled period of the Phase 3 trials, no deaths occurred while 4 deaths occurred in subjects while receiving study drug and considered not related to study drug. The other 2 deaths were considered non-treatment emergent (cerebral hemorrhage – unlikely related, and abnormal blood count - unrelated). Deaths are described in more detail in sections 7.3.4 of this review. Treatment with certolizumab was not associated with an increased incidence of treatment-related adverse reactions in the categories of congestive heart failure, cytopenias, and lupus-like disorders.

During the placebo-controlled period of the Phase 3 trials, SAEs occurred in 4.7% of subjects treated with certolizumab 400mg, 1.4% of subjects treated with certolizumab 200mg, 4.5% of subjects treated with placebo. Exposure adjusted rates of SAEs during the placebo-controlled period was 15.62 per 100 subject years in the certolizumab 400mg group, 4.73 per 100 subject years in the certolizumab 200mg group, and 15.4 per 100 subject years in the placebo group.

During the placebo-controlled period, the most common adverse reactions (AR) in subjects treated with certolizumab 400mg were upper respiratory infections (21.9%), headache (3.8%), injection site reactions (3.2 %), cough (3.2%), and herpes infection (1.5%). The frequency of AR was similar across all age and demographic groups. These are discussed in more detail in section 7.3.4 of this review. These AR are recommended to be included in Section 6 (Adverse Reactions) of certolizumab labeling.

Among subjects receiving certolizumab in the development program through August 29, 2017, there were 9 pregnancies in 8 subjects: 3 pregnancies reported in the Phase 2 studies (C870404 and C87044) and 6 pregnancies in the Phase 3 trials/extension. Pregnancy outcomes included 4 cases of fetal loss (1 spontaneous abortion and 3 elective abortions) and 1 pending pregnancy outcome. The effect of certolizumab on human reproduction and pregnancy is discussed in further detail in section 7.3.4 of this review. Because the available data is insufficient to inform certolizumab-associated risk in pregnant women, we will require post-approval prospective and retrospective studies assessing maternal, fetal, and neonatal outcomes of women exposed to certolizumab during pregnancy compared to an unexposed control population. Refer to Section 12 Postmarketing Requirements and Commitments for further details.

The safety data currently available demonstrate that certolizumab is safe for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Postmarketing risk management will include professional labeling (including a Medication Guide), prescription status, and routine pharmacovigilance. The maternal, fetal, and infant outcomes of women exposed to certolizumab during pregnancy will be evaluated by a registry based observational exposure cohort study.

7.4. Summary and Conclusions

7.4.1. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects for both doses of Cimzia were large and generally consistent across trials and endpoints. There were no substantial differences in efficacy among subgroups. For subjects with baseline PGA score of 3 (moderate) and baseline weight ≤ 90 kg, the treatment effect for Cimzia 200 mg was similar to Cimzia 400 mg (see Section 7.2.7.2). The amount of missing data was relatively small (<10%) at Week 16 (i.e., the primary efficacy timepoint), and the results were similar across the various methods investigated to impute the missing data (see Table 17).

7.4.2. Conclusions and Recommendations

To establish the effectiveness of Cimzia, the applicant submitted data from three randomized, multicenter, placebo-controlled, parallel-group, Phase 3 trials (Trials PS0002, PS0005 and PS0003). The trials enrolled subjects 18 years of age and older who had plaque psoriasis with PASI score ≥ 12, PGA score of ≥3 (moderate) and BSA of involvement of ≥10%. For Trials PS0002 and PS0005, the co-primary efficacy endpoints were the proportion of subjects achieving a PGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline at Week 16 and the proportion of subjects achieving PASI 75 at Week 16. These endpoints were specified as secondary efficacy endpoints for Trial PS0003 (i.e., the protocol-specified primary efficacy endpoint was PASI 75 at Week 12). In all three trials, both doses of Cimzia were statistically superior to placebo (p-values < 0.001) for PGA response at Week 16 and PASI 75 at Week 16 (see Table 15 and Table 16 in Section 7.2.4).

Trial PS0003 included etanercept as an active comparator and the protocol specified a single secondary efficacy endpoint against etanercept (i.e., PASI 75 at Week 12). Because the applicant did not establish an adequate scientific bridge between U.S. licensed Enbrel and EU approved etanercept, these products are considered distinct products for the purpose of this review. Table 16 in Section 7.2.4 presents the results for the secondary efficacy endpoint against etanercept in the overall population (all sites) and by country (U.S. vs. Non-U.S.) for Trial PS0003. In the overall population, Cimzia 400 mg was statistically superior to etanercept (p-value = 0.015); however, Cimzia 200 mg was not statistically superior to etanercept in the overall population (p-value = 0.152). In the U.S. only subgroup, both doses of Cimzia were not statistically superior to etanercept (p-values ≥ 0.846).

To support the safety of certolizumab, the applicant pooled data from the Phase 3 trials with data from the Phase 2 trials (C87040 and C87044). The applicant conducted a comprehensive assessment of the safety of certolizumab in the target population. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions.

Safety and efficacy data submitted by the applicant support approval of this BLA for certolizumab for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy

8 Advisory Committee Meeting and Other External Consultations

This efficacy supplement was not presented to the Dermatology Drug Advisory Committee because no safety or efficacy issues were identified that would warrant advisory committee input.

9 Pediatrics

No pediatric subjects were included in this efficacy supplement.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administrations 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, differed, or inapplicable. Because the submission proposes a new indication, the applicant was required to submit Initial Pediatric Study Plan (iPSP) under the IND.

Refer to the following sections of this review for the proposed development program for certolizumab in the pediatric population:

- Section 7.3.8 "Pediatrics and Assessment of Effects on Growth" for a discussion regarding the Pediatric Study Plan
- Section 12 "Postmarketing Requirements and Commitments for the deferred pediatric studies, which are required under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)).

10 Labeling Recommendations

10.1. Prescribing Information

The applicant submitted proposed Prescribing Information (PI) and carton/container labels for CIMZIA (certolizumab pegol) injection. The review team provided recommendations regarding PI which are provided throughout this review. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI and Medication Guide. These comments are reflected in final labeling. Refer to the OPDP review by Jina Kwak, PharmD (dated 4/6/18) and DMPP review by Shawna Hutchins, MPH, BSN, RN (dated 4/13/18). Labeling negotiations are currently ongoing.

The following table provides the location of the labeling discussion for each section.

Summary of Significant High Level Labeling Changes	
Section	**Location of Reviewer Comments on Proposed Labeling**
1 INDICATIONS AND USAGE	Section 1.1, 5.6
2 DOSAGE AND ADMINISTRATION	Section 6.3
4 CONTRAINDICATIONS	Section 7.3.5
5 WARNINGS AND PRECAUTIONS	Section 7.3.4, 7.3.5
6 ADVERSE REACTIONS	Section 6.2, 7.3.4, 7.3.5
8 USE IN SPECIFIC POPULATIONS	Section 6.3
12 CLINICAL PHARMACOLOGY	Section 6
14 CLINICAL STUDIES	Section 7
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling.

10.2. Patient Labeling

The applicant submitted a proposed medication guide (MG). The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments on the proposed MG for CIMZIA (certolizumab pegol) injection, for subcutaneous use. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Shawna Hutchins, MPH, BSN, RN (dated 4/13/2018) for comments regarding the MG.

11 Risk Evaluation and Mitigation Strategies (REMS)

Risk mitigation measures beyond professional labeling and a Medication Guide are not warranted at this time. Under 21CFR208.1, the Medication Guide is required to help prevent serious adverse effects. See Section 10.1 Labeling Recommendations. As no additional risk management strategies are required, the subsequent subsections are not applicable for this review and are omitted.

12 Postmarketing Requirements and Commitments

Clinical postmarketing requirements are intended to characterize the risks of certolizumab use in special populations and address the long- term safety of this novel biologic product in the target population. Agreed postmarking quality commitments are summarized in this section and discussed in Section 6.2.1.

Pediatric Research Equity Act (PREA) applies to this efficacy supplement. (b) (4) [redacted]

Based on review of the data in this submission, the following postmarketing requirements (PMRs) and commitments (PMCs) were conveyed to the applicant:

POSTMARKETING REQUIREMENTS UNDER 505(o)

REQUIRED PEDIATRIC ASSESSMENTS: Pediatric Research Equity Act (PREA) (21 U.S.C. 355c)

We are waiving the pediatric study requirement for ages 0 to less than 6 years because necessary studies are impossible or highly impracticable. This is because:

- The prevalence of psoriasis in the 0 to less than 6 years age group is low (with the highest prevalence published of 0.3%) and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.

- Live vaccinations (MMR, varicella) are usually given in this age group, limiting the treatment of this pediatric population with certolizumab.

We are requiring submission of pediatric studies for the pediatric plaque psoriasis population ages 6 years to less than 18 years for this application. The required study is listed below.

PMR 3408-1
Conduct a Pharmacokinetics (PK), Safety, and Efficacy Study in pediatric subjects 6 to <18 years of age with moderate to severe psoriasis (with a duration of exposure to certolizumab pegol of at least one year).

Final Protocol Submission:	06/2019
Study/Trial Completion:	02/2025
Final Report Submission:	12/2025

The following PMR (3408-2) and related PMCs (3408-5 and 3408-6) are recommended by the Clinical Pharmacology and Office of Biotechnology teams. Refer to Section 6 for further discussion.

PMR 3408-2

Utilize the validated immunogenicity assays developed under PMC 3408-5 and PMC 3408-6 to analyze the immunogenicity profile of certolizumab pegol using banked patient samples from Phase 3 trials CIMPASI-1, CIMPASI-2, and CIMPACT. Evaluate the impact of immunogenicity on pharmacokinetics, efficacy, and safety in subjects with psoriasis based on the immunogenicity data generated with the newly validated assays.

Final Protocol Submission:	12/31/2018
Study/Trial Completion:	06/30/2019
Final Report Submission:	09/30/2019

PMC 3408-5

Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to certolizumab pegol, including procedures for the accurate detection of binding antibodies to certolizumab pegol in the presence of certolizumab pegol levels expected in the serum or plasma at the time of patient sampling. In addition, an assessment of the contribution of binding antibodies to PEG should also be evaluated.

Final Report Submission:	06/30/2018

PMC 3408-6

Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to certolizumab pegol, including procedures for the accurate detection of neutralizing antibodies to certolizumab pegol in the presence of certolizumab pegol levels that are expected in the serum or plasma at the time of patient sampling.

Final Report Submission:	06/30/2018

The available safety data regarding certolizumab use during pregnancy is limited. The study population as defined by the entry criteria excluded pregnant and breastfeeding females, and females planning to become pregnant or breastfeed during the trials. The

applicant reported that 9 pregnancies occurred in female subjects exposed to certolizumab. Because human IgG antibodies are known to cross the placental barrier and exposures to certolizumab during pregnancy are likely to occur, the applicant will be required to conduct the postmarketing assessments (5-6) described below to characterize the drug associated risk.

PMR 3408-3

A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to certolizumab pegol during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, will be assessed through at least the first year of life. You may expand a current prospective registry to include women who are exposed to certolizumab pegol for the treatment of plaque psoriasis.

Final Protocol Submission:	12/2019
Study/Trial Completion:	07/2029
Final Report Submission:	01/2030

PMR 3408-4

Conduct a retrospective cohort study using claims or electronic medical record data or a case control study to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths, and infant infections in women exposed to certolizumab pegol during pregnancy compared to an unexposed control population.

Final Protocol Submission:	02/2020
Study/Trial Completion:	09/2026
Final Report Submission:	09/2027

13 Appendices

13.1. References

The references are included in footnotes throughout the document.

13.2. Financial Disclosure

The covered clinical studies as defined in 21 CFR 54.2(e) were Trials PS0005, PS0002, and PS0003, which provided the primary data to establish effectiveness and safety of this product. Refer to Section 7.2.1 for the trial designs.

Covered Clinical Study (Name and/or Number): PS0005

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 30		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

For Trial PS0005, 4 sub-investigators did not have signed financial disclosure form (FDF) for UCB because it was not included in the essential document list. This essential document list

was corrected and attempts made to obtain signed FDFs but the above individuals no longer worked at the trial sites.

Covered Clinical Study (Name and/or Number): PS0002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 27		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

For Trial PS0002, 3 sub-investigators and 1 site coordinator did not have signed financial disclosure form (FDF) for UCB because it was not included in the essential document list. This essential document list was corrected and attempts made to obtain signed FDFs but the above individuals no longer worked at the trial sites.

Covered Clinical Study (Name and/or Number): PS0003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 57		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Clinical/Biostatistics

Table 34: Physician's Global Assessment of Psoriasis (PGA)

Score	Short Descriptor	Description
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost Clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep red dark coloration; severe/coarse scaling covering almost all or all lesions

Source: protocols for Trials PS0002, PS0005 and PS0003

Figure 19: Psoriasis Area Severity Index (PASI)

The PASI score is calculated in the following manner. The body is divided into 4 sections (head (h) (10% of a person's skin); arms (a) (20%); trunk (t) (30%); legs (l) (40%)). Each of these sections is scored by itself, and then the 4 scores are combined into the final PASI. For each section, the percent of area of skin affected (A), is estimated and then transformed into a grade from 0 to 6:

- 0% of involved area, grade: 0
- < 10% of involved area, grade: 1
- 10-<30% of involved area, grade: 2
- 30-<50% of involved area, grade: 3
- 50-<70% of involved area, grade: 4
- 70-<90% of involved area, grade: 5
- 90-100% of involved area, grade: 6

Within each section, the severity is estimated by three clinical signs: redness (R), thickness (T) and scaling (S). Severity is measured on a scale from 0 to 4 (0 = none and 4 = very marked).

The PASI is a measure of the average redness, thickness, and scaliness of the psoriatic skin lesions, multiplied by the involved psoriasis area score of the respective section, and weighted by the percentage of the person's affected skin for the respective section. Scores for each body part for redness, thickness and scaling and the percentage of skin covered with PSO will be entered into the Electronic Case Report Form (eCRF). The following formula is used to calculate the PASI:

PASI = 0.1 x (Rh+Th+Sh) x Ah + 0.2 x (Ra+Ta+Sa) x Aa +0.3 x (Rt+Tt+St) x At +0.4 x (Rl+Tl+Sl) x Al

Source: statistical analysis plan (SAP) for Trials PS0002, PS0005, and PS0003

13.4. Nonclinical Pharmacology/Toxicology

None.

13.5. OCP Appendices (Technical documents supporting OCP recommendations)

13.5.1. Summary of Bioanalytical Method Validation and Performance of the PK assays

Historically, the Applicant used a validated enzyme-linked immunosorbent assay (ELISA) assay coupled with a colorimetric readout ((b) (4) method ELISA-0168) with a LLOQ of 0.412 mcg/mL. This old assay was also used for the Phase 2 studies in subjects with psoriasis. This assay along with its related validation reports (Method Validation Report 7213-110 and addendums) have been previously reviewed under the original BLA and were found to be acceptable.

Subsequently, the Applicant developed and validated a more sensitive method (LLOQ of 0.032 mcg/mL) using an electrochemoluminescence (ECL) assay on a Meso Scale

Discovery® (MSD) platform to quantify CZP plasma concentrations. The ECL assay with improved sensitivity was used for the quantification of CZP levels in all three Phase 3 studies in psoriasis subjects. The assay format involved adding diluted TNF-alpha to the wells of an MSD plate and incubating overnight at 2 to 8°C, followed by blocking with PBS/1% BSA/0.5% Non-Fat Dried Milk (NFDM) after washing. Then, calibrators, controls and samples (diluted to a 1/100 MRD) were added to the plate and incubated for 1 hour, followed by washing. A further incubation with biotinylated Rabbit anti-PEG for 1 hour was followed by washing. MSD Sulfo-TAG Streptavidin conjugate was then added for 1 hour, followed by washing. Finally, 2x Read Buffer was added to each well and the plate was read on MSD Sector Imager 6000.

The validation parameters of both these assays are summarized in Table 35.

Table 35: Summary of method validation parameters for assays for measurement of CZP concentrations in human plasma.

Assay Method	ECL assay	ELISA with colorimetric readout
Bioanalytical method validation reports	Method Validation Report 8294-355, Method Validation Report 8294-355 Addendum 1, and Method Validation Report 8294-355 Addendum 2	Method Validation Report 7213-110, Method Validation Report 7213-110 Addendum 1, and Method Validation Report 7213-110 Addendum 2
Test reference standard	Test article CZP (Lot # B236873)	Test article CZP (Lot # B093676)
Calibration range	0.032 to 5.00µg/mL	0.412 to 33.3µg/mL
Within run precision (% CV)	4.4% to 26.6% at LLOQ 4.2% to 21.2% at LQC 2% to 19.5% at MQC 2.9% to 18.5% at HQC 4% to 18.6% at ULOQ	11.5% to 77.1% at LLOQ 3.63% to 8.68% at LQC 0.431% to 10.3% at MQC 3.02% to 16.7% at HQC 5.23% to 8.15% at ULOQ
Between run precision (% CV)	13.2% to 17.5% for QC levels; 12.7% to 22.2% at LLOQ and ULOQ	6.10% to 10.8% for QC levels (32.5% at LLOQ)
Within run accuracy (% Bias)	-17.4% to 20.7% for QC levels; -19.1% to 18.1% at LLOQ and ULOQ	98.2% to 105% for QC levels (66.6% at LLOQ) (% AR)
Between run accuracy (% Bias)	-7.6% to 2.6% for QC levels; 0.9% at LLOQ; -5.6% at ULOQ	96.8% to 105% for QC levels (66.6% at LLOQ) (% AR)
Total error (%)	17.0% to 20.8% for QC levels; 18.3% to 23.1% at LLOQ and ULOQ	65.9% (LLOQ); 11.4% (ULOQ)
Hook Effect	No hook effect was observed.	No hook effect was observed.
Dilution linearity	Linear from 1:10 to 1:640	Linear from 1:5 to 1:40

Selectivity (in plasma from psoriasis subjects)	Bias: -19.6% to 19.8% % CV < 25%	NA
Freeze thaw stability	15 freeze/thaw cycles	9 freeze/thaw cycles
Bench-Top Stability	90 hours at room temperature (ca. 20°C)	48 hours at room temperature
Long Term Storage Stability	31 months and 14 days at -60°C to -80°C	772 days at -60°C to -80°C

(*Source of Data: Table 1-1 from summary of biopharmaceutic studies and associated analytical methods and method validation reports from the respective assays*)

The Applicant conducted a cross-validation study (Method Validation Report 8294-355) which demonstrated that the previous colorimetric method and the ECL method used in the Phase 3 psoriasis studies are comparable. To assess consistency across the newer ECL method and the previous method, six normal plasma samples were spiked at 1.000 µg/mL (LQC), 8.000 µg/mL (MQC), 24.000 µg/mL (HQC), and an ultra-high QC level (UHQC) of 50.000 µg/mL. These samples were subsequently tested in triplicate in two different assay runs of each of the two methods. A total of seven of 24 spiked samples returned values with greater than 20% difference between the methods. However, a total of 20 (87.5 %) out of 24 control samples were within ≤30% for percent difference in concentration between the two studies. In considering the criterion recommended for Incurred Sample Reanalysis (ISR) assessment, the two methods used for the quantification of CZP in human serum can be considered comparable.

The in-study bioanalytical report for the Phase 3 studies showed that the performance of the calibration standards was acceptable with acceptable accuracy and % CV ranging from 2.1% to 9.2 %. The mean bias for QCs ranged between -2.7% to 6.1 % and the CV% were <24%. The ISR analysis for all three studies were also acceptable with at least 80 % of repeated sample results were within 30 %.

Overall, the bioanalytical method for measuring serum CZP concentrations is considered acceptable.

13.5.2. Population PK and E-R analysis

Summary of Findings

In the current submission, the applicant proposed to use certolizumab pegol to treat subjects with moderate to severe chronic plaque psoriasis (PSO). The proposed dosing regimen is 400 mg every other week. The proposed dosing regimen also states that a dose of 400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week may be considered.

Based on the totality of the data, both 200 mg and 400 mg Q2W demonstrated significant efficacy benefit compared to the placebo and tolerable safety profile.

However, 400 mg Q2W showed a numerically better response rates compared to 200 mg Q2W (9% higher for PGA, 8% higher for PASI90 and 5% higher for PASI75) (Figure 20). Our analyses suggest that the discrepancy of efficacy between these two dosing regimens is likely due to the higher anti-drug antibody (ADA) production rate in low dose group (especially in patients with the higher body weight) (Figure 27, Table 38). Thus, 200 mg should not be recommended for patients with high body weight. ADA production has significant effect on certolizumab pegol exposure and efficacy (Figure 21, Figure 23). In ADA positive patients, certolizumab pegol clearance was increased by approximately 3 fold. The population average exposure has dropped below 2.4 µg/mL, which is far below EC90 (11.1 µg/mL) predicted by PK-PD model (Figure 28). The PASI 75 response rate in ADA positive patients is around 25%-50% which is significantly lower than the 70%-84% in ADA negative patients (Figure 23).

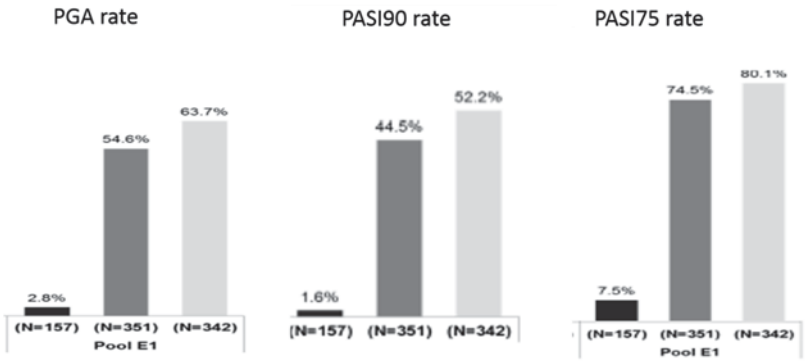
ADA production rate is higher in the low dose (200 mg) treatment group (especially in patients with the higher body weight). Population pharmacokinetic (popPK) model suggests there is a linear relationship between BW vs. clearance (Figure 24, Table 39). Thus, under the circumstance of flat dose regimen, patients with the heavy body weight at the low dose (200mg) will have an insufficient certolizumab exposure. The ADA positive rate decreased to around 9% in heavy patients at the 400 mg dose (Figure 27). This lead to around 10% increase in efficacy in high body weight subgroup by using 400 mg Q2W dosing regimen compared with 200 mg Q2W. Meanwhile the gain of efficacy in low body weight subgroup is less obvious (around 4%). The safety profiles in the body weight subgroups in the two dosing regimens are comparable, which is consistent with the overall lack of the dose-safety relationship. In summary, although both the dosing regimens are efficacious for the treatment of patients with chronic plaque psoriasis, 200 mg is not recommended for patients with high body weight (>=90 kg).

Key Review Questions

Is proposed dose appropriate in general population?

Yes. Three phase 3 studies had been conducted: CIMPASI-1, CIMPASI-2 and CIMPACT. Both 200 mg and 400 mg dosing regimens have showed significant benefit on efficacy based on PGA, PASI 75 and PASI 90 response rates (Figure 20). A numerical better on efficacy is observed in the 400 mg Q2W dosing regimen. The incidences of treatment-emergent adverse events (TEAEs) in Pool S1 (Initial Treatment Period of the Phase 3 studies) were generally similar between the CZP 400 mg Q2W and the placebo groups (63.5% and 61.8%, respectively) and were lower in the CZP 200mg Q2W group (56.3%). The most frequently reported TEAE in the two CZP dose groups was nasopharyngitis; the incidences were similar to the placebo group. Thus, based on the totality of the data, both dosing regimens are acceptable for the indication of PSO.

Figure 20. Overall Response in Pooled 3 Studies



Source: Figure 4.1 of clinical overall. Placebo (Black), 200 mg (dark gray) and 400 mg (light gray) groups. The black bar is placebo; the dark grey bar is 200 mg dosing level and the light grey bar is 400 mg dosing level.

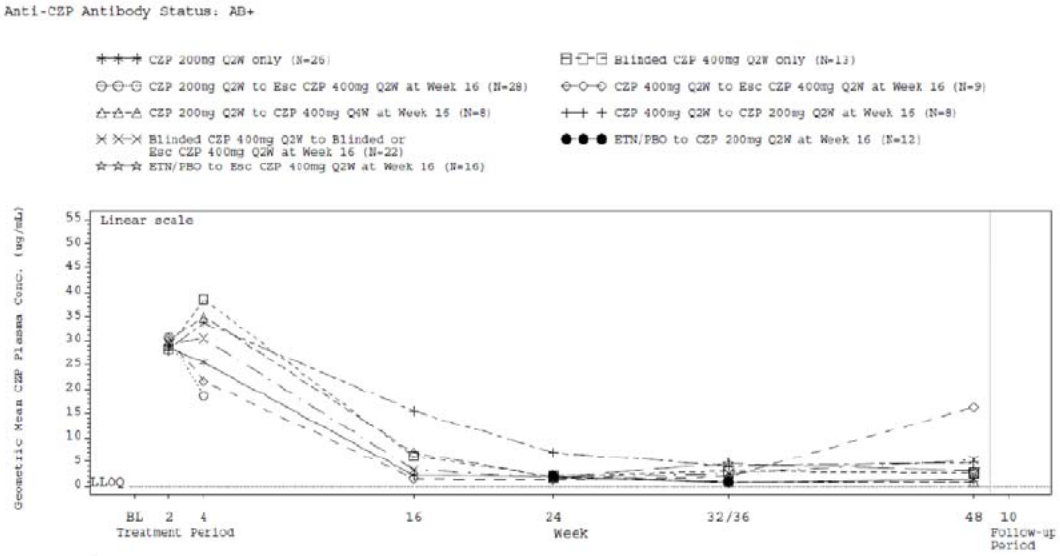
What is the effect of Anti-Drug Antibody on Exposure and Efficacy?

ADA production has significant effect on certolizumab pegol exposure and efficacy. In ADA positive patients, certolizumab pegol exposure has dropped below 2.4μg/mL (Figure 21 and

Figure 22), which is far below EC90 (11.1 μg/mL) predicted by PK-PD model (Figure 28).

Figure 21 showed certolizumab pegol concentration in ADA+ patients in different arms. Most ADA production time was between week 4 and week 16. Very few patients were detected to be ADA+ at week 4. Since there is no blood sample collected between week 4 and week 16, specific time for ADA production is unknown. From the Figure 21, we could see at population level, ADA+ patients' clearance increased by approximately 3 fold and the exposure is dropped significantly.

Figure 21. Plasma Certolizumab Pegol Concentration in ADA+ Patients in Different Arms



AB=antibody; ADAb=anti-drug antibody; BL=Baseline; conc.=concentration; CZP=certolizumab pegol; Esc=escapers; ETN=etanercept; ISS=Integrated Summary of Safety; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks
Data source: ISS Figure 3.1.2

Source: Figure 3-2 of summary of clinical pharm report

Representative individual plot for ADA+ subject was generated and shown in

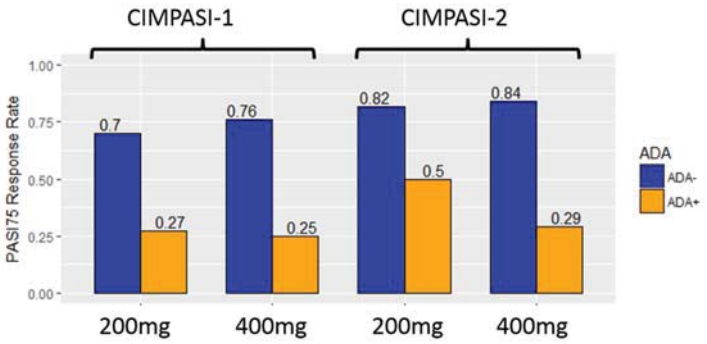
Figure 22. Each purple dot is a PK observation. Red region is ADA positive period. Vertical bar showed the dosing schedule, blue bar indicates a 400mg dosing and the red bar indicate a 200mg dosing. Horizontal black line is the 11.1ug/ml EC90 line, below which means there should be a compromise on efficacy. PGA categorical variable (not PGA score) beside the subject ID indicate whether the individual is a PGA responder (1) or a PGA non-responder (0) at week 16. A full individual plot for ADA+ patients is shown in Figure 29. From individual plot, we could see the effect of ADA on certolizumab pegol exposure.

Figure 22. Plasma CZP profiles in individuals who are ADA positive

Source: FDA reviewer's independent analysis. X-axis is time (weeks). Y-axis is certolizumab pegol drug concentration (µg/mL). Each purple dot is a PK observation. Red region is ADA positive period. Vertical bar showed the dosing schedule, blue bar indicates a 400 mg dosing and the red bar indicate a 200mg dosing. Horizontal black line is the 11.1ug/mL EC90 line, below which means there should be a compromise on efficacy. PGA of 1 or 0 beside the subject ID is a categorical variable (not PGA score) indicating whether the individual is a responder (PGA=1) or a non-responder (PGA=0) at week 16.

The PASI 75 response rate in ADA positive patients is around 25%-50% compared with 70%-84% in ADA negative patients (Figure 23). From the subgroup analysis in CIMPASI-1 and CIMPASI-2, we could further see that there is no difference on PASI75 response rate between two dosing regimens if ADA status is stratified.

Figure 23. PASI75 Response Rate Stratified by ADA Status

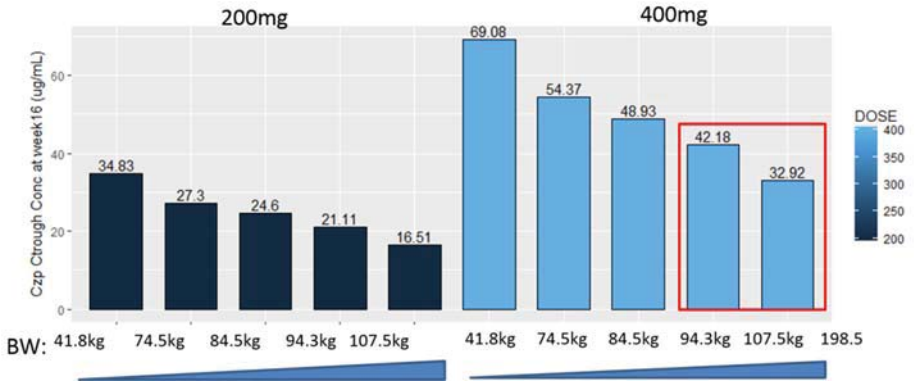


Source: Adapted from Subgroup Analysis of CRS

What is the Effect of Body Weight on exposure and Efficacy?

For a given dose treatment, patients with high body weight are likely to have a lower exposure, and therefore a lower efficacy (especially in the low dose of 200 mg group). PopPK model suggests there is a linear relationship between BW vs. clearance with an exponent of 0.942 (Figure 24 and Table 39). Thus, under the circumstance of flat dose regimen, the low dose (200 mg) in the high body weight subgroup has a lower average exposure. The ADA positive rate decreased to around 24% in heavy patients at the 400 mg dose (Figure 27). This lead to around 10% increase in efficacy in the high body weight subgroup by using the 400 mg Q2W dosing regimen compared with the 200 mg Q2W (Figure 25). Meanwhile the gain of efficacy in the low body weight subgroup is less obvious (around 2%-6%). The safety profiles in both body weight subgroups with the two dosing regimens are comparable, which is consistent with the overall lack of the dose-safety relationship (Table 36).

Figure 24: Body Weight Effect on Exposure

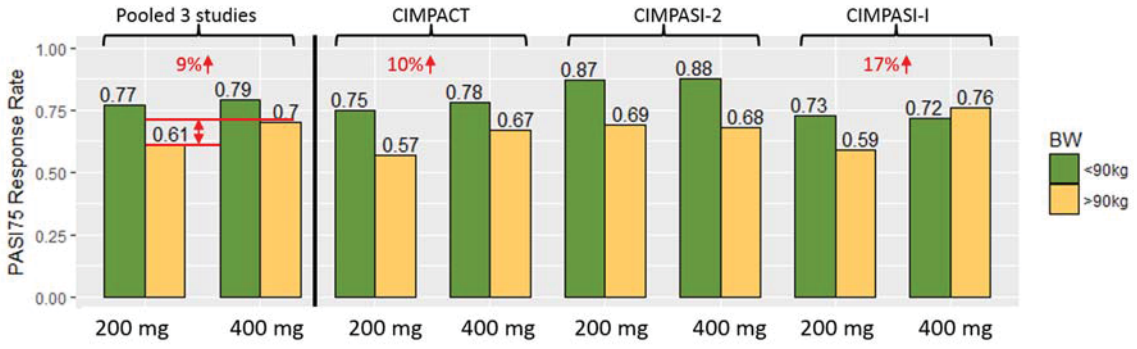


Source: Adapted from Table 10 from Pop-PK Report

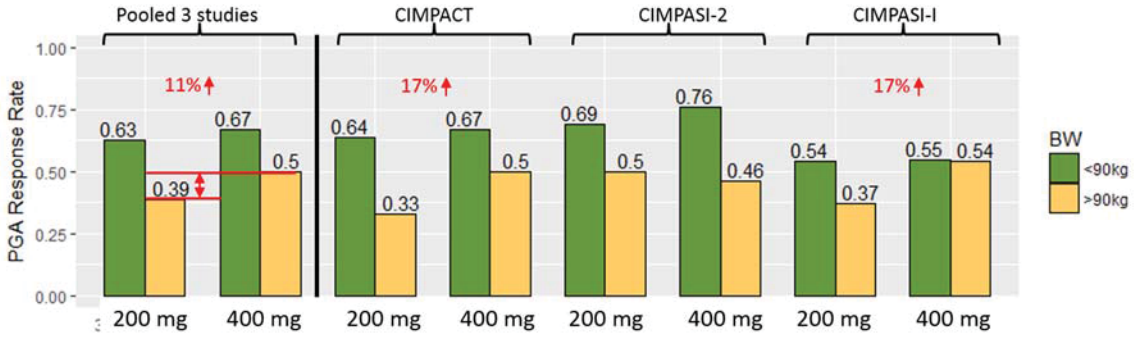
Body Weight subgroup analysis showed the positive dose-response relationship in the higher body weight subgroup (BW > 94.3 kg) in pooled 3 studies and each study (Figure 25) There is no obvious difference of the safety profile in body weight subgroup analysis (Table 36). This result is consistent with overall flat dose safety result.

Figure 25: Dose Efficacy Relationship in Body Weight Subgroups at Week 16

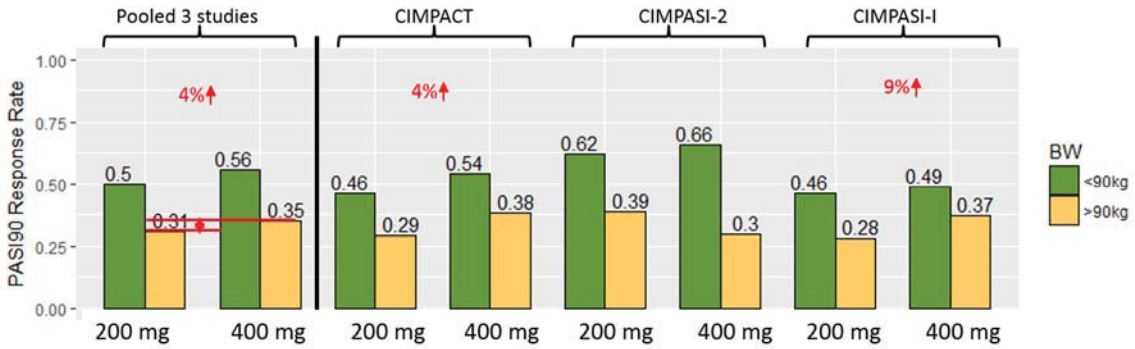
(A) PASI75 Response Rate at Week 16



(B) PGA Response Rate at Week 16



(C) PASI90 Response Rate at Week 16



Source of data: Reviewer generated plot based on Applicants response to RFI dated 25th Jan 2018)

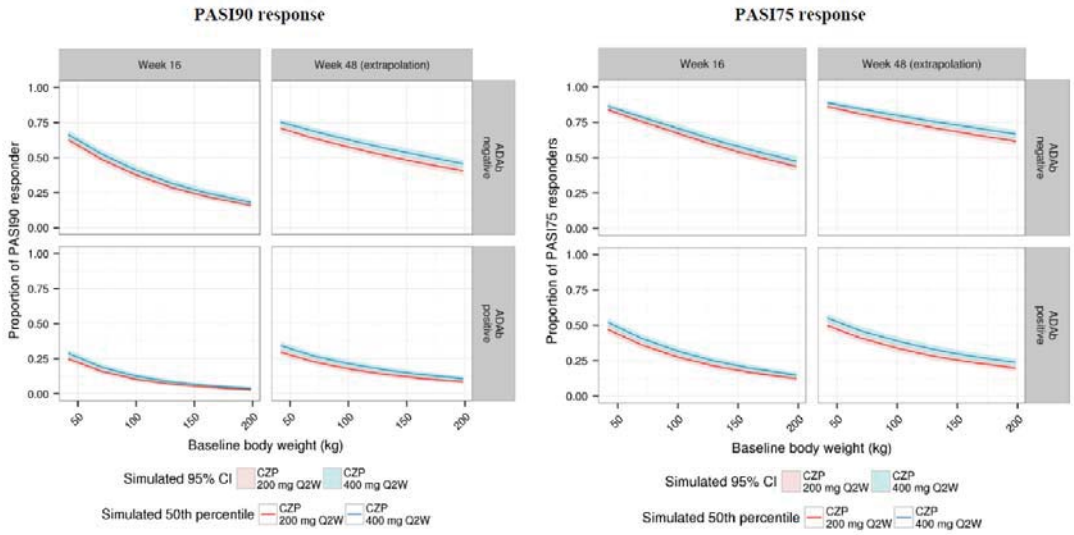
Table 36: Safety Profile Based on Body Weight Subgroups

AE	Placebo(N=157)		CIMZIA 400mg Q2W (N=342)		CIMZIA 200mg Q2W (N=350)	
	BW<100 (N=110)	BW>=100 (N=47)	BW<100 (N=254)	BW>=100 (88)	BW<100 (N=233)	BW>=100 (N=117)
Nasopharyngitis*	17 (15%)	4 (9%)	35 (14%)	14 (16%)	35 (15%)	12 (10)
Headache	2 (1.8%)	1 (2.1%)	11 (4.3%)	2 (2.3%)	8 (3.4%)	2 (1.7%)
Viral upper respiratory tract infection	1 (0.9%)	0	7 (2.76%)	1 (1.11%)	4 (1.7%)	4 (3.4%)
Cough	3 (2.7%)	0	11 (4.3%)	0	3 (1.3%)	1 (0.9%)
Pharyngitis	0	0	3 (1.2%)	1 (1.1%)	5 (2.1%)	1 (0.86%)
Urinary tract infection	2 (1.8%)	0	3 (1.2%)	2 (2.3%)	1 (0.4%)	3 (2.6%)
Oropharyngeal Pain	0	0	3 (1.2%)	1 (1.1%)	3 (1.3%)	1 (0.9%)

Source: Reviewer's Analysis

An indirect PKPD modeling and simulation showed that, after adjustment of body weight and ADA status on PASI 75 and PASI 90, there is very limited gain on efficacy between 200 mg Q2W vs. 400 mg Q2W dosing regimens indicated by red line and blue line under same body weight and ADA status (Figure 26). Thus, the discrepancy we observed in high body weight subgroup between 200 mg and 400 mg Q2W are likely due to the lower ADA+ rate in higher dose.

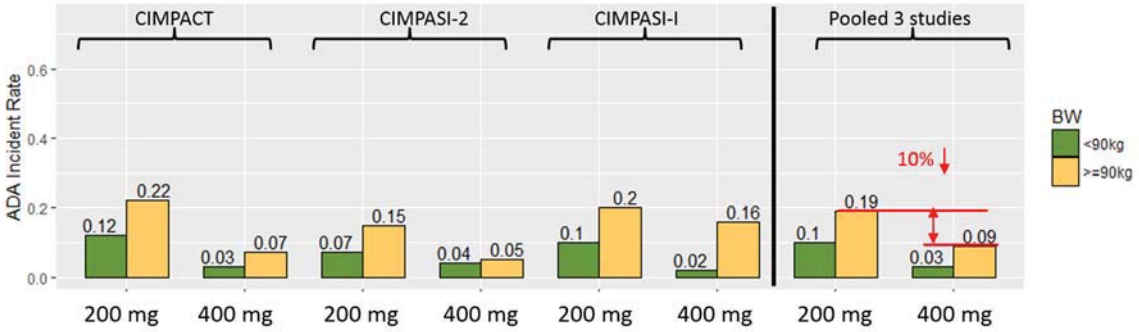
Figure 26: Effect of Body Weight and Anti-Drug Antibody on Efficacy Predicted by PKPD Model



Source: Figure 3-4 of summary of clinical pharm.

A reversed exposure-ADA incident rate relationship was identified. Since body weight influences the exposure, a significant higher incident rate of ADA was found in high body weight subgroup (especially with the 200 mg dose) (Figure 27). The effect of ADA on exposure and efficacy is discussed in previous sections.

Figure 27: Anti-Drug Antibody Incident Rate in Body Weight Subgroups



Source: Reviewer's Analysis

A logistic regression and simulation on ADA production rate based on BW and certolizumab pegol dose were conducted.

$$\text{Logit (ADA production rate)} = \text{Intercept} + BW*b1 + \text{Dose(400mg)} *b2$$

And the regression result is shown in Table 37.

Table 37: Logistic Regression Parameters of ADA Production Rate Vs. Body Weight and Dose

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-2.856	0.446	-6.407	0.000
b1 (B2)	0.017	0.004	3.845	0.000
b2 (DOSE 400 mg)	-0.615	0.212	-2.904	0.004

A model simulated ADA production rate based on body weight and dose (200 mg and 400 mg) was presented in Table 38.

Table 38: Model Predicted ADA Production Rate Based on BW

BW (kg)	DOSE (mg)	fit	high	low
70		0.16	0.21	0.12
80		0.18	0.23	0.14
90		0.21	0.26	0.17
100	200 mg	0.24	0.29	0.19
120		0.30	0.38	0.24
150		0.42	0.55	0.30
190		0.59	0.77	0.38
70		0.09	0.13	0.06
80		0.11	0.15	0.08
90		0.12	0.16	0.09
100	400 mg	0.14	0.19	0.11
120		0.19	0.26	0.14
150		0.28	0.41	0.18
190		0.44	0.65	0.24

Source: reviewer's independent analysis.

Recommendations

The Office of Clinical Pharmacology agrees with the proposed dosing regimen of 400 mg every other week and recommend that a dose of 400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week may be considered for some patients with a low body weight (<90 kg).

RESULTS OF APPLICANT'S ANALYSIS

PK Model

The PK characteristics of CZP in patients with PSO were well described by a one compartment model with first-order absorption and a first-order elimination from the central compartment. The impact of the covariates age, body mass index (BMI), body

surface area (BSA), body weight (WT), anti-CZP antibodies (ADAb) and sex were evaluated in the covariate analysis of the PK model. It was concluded that WT affects apparent clearance (CL/F) and apparent volume of distribution (V/F) and CL/F is increased by approximately 3-fold in ADAb positive subjects (with ADAb>2.4 U/mL). Therefore, CZP exposure decreased with increasing WT and ADAb positive subjects generally have lower CZP concentration than ADAb negative subjects (ADAb_2.4 U/mL).

Table 39: Parameter Estimates of the Base Reference PK CZP Model

		Base reference PK model for CZP		
Run		155		
OFV		24643.58		
Condition number		23.25		
		Base reference PK model for CZP		
	Unit	**Value**	**RSE (%)**	**SHR (%)**
k_a	day^{-1}	0.247	4.87	
CL/F	L/day	0.338	1.37	
V/F	L	4.68	2.05	
F		1.00	(FIX)	
ADAb impact on CL/F		2.30	12.4	
WT impact on V/F		0.508	11.3	
WT impact on CL/F		0.942	3.86	
IIV CL/F	(% CV)	22.0	3.35	9.12
IIV V/F	(% CV)	15.0	16.4	59.0
Prop. Err.	(%)	16.9	7.82	9.58
Add. Err.	(µg/mL)	5.11	9.45	9.58

Source: Table 6 of Pop-PK Report.

PASI model and Simulation

The final PASI model was an indirect effect model. This type of model allows a delay between beginning of the treatment (placebo or CZP) and appearance of the response and was therefore well suited for the population PKPD analysis of PASI. The Placebo effect had an impact on Kin resulting in an increase or decrease in PASI as a function of time since the treatment commenced. The CZP induced effect was characterized by a sigmoid Emax model using the individual Cipred as predictor of the response. The baseline PASI was modeled in the logit domain to ensure the baseline PASI boundaries of 12 and 72, defined as an inclusion criterion in the protocol, were accounted for. The Placebo effect and Emax were also modeled in the logit domain to ensure that the maximum total effect of placebo and of CZP treatment did not exceed 100%. The boundary of the maximum placebo induced increase in PASI (an unfavorable effect) was set to 150% (Placebo effect = -1.5). This boundary was defined based on the observed data. The PASI observations were modeled in the logit domain to constrain the model predictions to the limits of the PASI scale (0 to 72). In the final model, IIV terms were supported on PASI baseline, Placebo effect, EC90 and PASI t1/2. The RUV was described by a combined error model (proportional and additive).

The covariate-parameter relationships included in the final PASI model were: prior treatment with biologics and region on PASI baseline; WT on Placebo effect; modeled PASI baseline on Emax; WT and region on PASI t1/2; and at least one ADAb event >2.4 U/mL during the first 16 weeks on EC90, where:

- Subjects previously treated with biologics had higher PASI at baseline.
- North American subjects had lower PASI baseline than Western European and Central/Eastern European subjects.
- North American subjects had a more rapid onset of the effect (shorter PASI t1/2) and Western European subjects had slower onset of the effect, compared to Central/Eastern European subjects.
- Subjects with a high WT had a slower onset of the effect (longer PASI t1/2) and smaller Placebo effect.
- Subjects with low PASI baseline values had lower CZP induced decrease in PASI than subjects with high baseline PASI values. Note that the effect magnitude was directly proportional to baseline before this covariate was included in the model.
- Subjects with at least one ADAb > 2.4 U/mL in the first 16 Weeks, had higher EC90 resulting in a reduced PASI response

Table 40: Final Parameter Estimates of the Final PASI Model

	Final PASI model
Run	2746
OFV	17121.3
Condition number	365.5

		Final PASI model	
	Unit	Value	RSE (%)
PASI baseline		19.0	2.29
PASI $t_{1/2}$	days	22.5	4.94
$Placebo_{effect}$		0.143	20.1
EC_{90}	µg/mL	11.1	47.3
Gamma (γ)		0.425	17.2
E_{max}[a]		0.974	0.228
Prior biologics on PASI baseline[b]		0.340	25.1
Region North-America on PASI baseline[b]		-0.323	24.7
PASI baseline on E_{max}[b]		0.0711	16.9
WT on $Placebo_{effect}$[b]		-0.00672	31.4
WT on PASI $t_{1/2}$		0.485	28.1
Region North-America on PASI $t_{1/2}$		-0.192	30.1
Region West-Europe on PASI $t_{1/2}$		0.216	64.8
ADAb16 positive on EC_{90}		47.7	28.8
IIV on PASI baseline[b]	(% CV)	91.0	4.33
IIV on PASI $t_{1/2}$	(% CV)	53.2	5.85
IIV on $Placebo_{effect}$[b]	(% CV)	71.3	9.99
IIV on EC_{90}	(% CV)	515	15.7
Prop. Err.	(%)	10.8	6.93
Add. Err.		0.233	5.81

Source: Table 13 of Pop-PK report

Figure 28: Predicted PKPD Relationship between PASI Score and Ctrough at Week 16

Source: Figure 33 of Pop-PK report

Reviewer's comments: The applicant's pop-PK model and indirect PKPD model is acceptable.

REVIEWER'S ANALYSIS

Objectives

Analysis objectives are:

To access the influence of anti-drug antibody on certolizumab pegol's exposure.

Methods

Data Sets

Data sets used are summarized in Table 41.

Table 41: Analysis Data Sets

Study Number	Name	Link to EDR
dat-11-pasi-ada-ucb-cimzia-pmx-5.csv	PK, ADA dataset	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Certolizumab pegol_BLA125160_YX\certolizumab pegol_plaque psoriasis\analysis

Software

R studio

Results

Individual plots for ADA+ subject are presented in Figure 29.

From the result of some individuals, we could see once the ADA is produced, PK dropped quickly to a very low level and the patients is more likely to be a non-responder.

In some 200 mg patients, once ADA is produced, PK could not be rescued by increasing dose to 400 mg (ID= (b) (6)).

Figure 29: Anti-Drug Antibody Positive Subjects Individual Analysis

(A) CIMPASI-2

Source: Reviewer's independent analysis. X-axis is time (weeks). Y-axis is certolizumab pegol drug concentration (µg/mL). Each purple dot is a PK observation. Red region is ADA positive period. Vertical bar showed the dosing schedule, blue bar indicates a 400 mg dosing and the red bar indicate a 200mg dosing. Horizontal black line is the 11.1ug/mL EC90 line, below which means there should be a compromise on efficacy. PGA score beside the subject ID indicate whether the individual is a responder (PGA=1) or a non-responder (PGA=0) at week 16.

(B) CIMPACT

Source: Reviewer's independent analysis. X-axis is time (weeks). Y-axis is certolizumab pegol drug concentration (µg/mL). Each purple dot is a PK observation. Red region is ADA positive period. Vertical bar showed the dosing schedule, blue bar indicates a 400 mg dosing and the red bar indicate a 200mg dosing. Horizontal black line is the 11.1ug/mL EC90 line, below which means there should be a compromise on efficacy. PGA score beside the subject ID indicate whether the individual is a responder (PGA=1) or a non-responder (PGA=0) at week 16.

(C) CIMPASI-I

Source: Reviewer's independent analysis. X-axis is time (weeks). Y-axis is certolizumab pegol drug concentration (µg/mL). Each purple dot is a PK observation. Red region is ADA positive period. Vertical bar showed the dosing schedule, blue bar indicates a 400 mg dosing and the red bar indicate a 200mg dosing. Horizontal black line is the 11.1ug/mL EC90 line, below which means there should be a compromise on efficacy. PGA score beside the subject ID indicate whether the individual is a responder (PGA=1) or a non-responder (PGA=0) at week 16.

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
CZP.R	Analysis code	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Certolizumab pegol_BLA125160_YX\certolizumab pegol_plaque psoriasis\analysis

APPENDIX:

Information Request for BLA125160 Certolizumab pegol supplement 283 for the treatment of adult patient with moderate to severe chronic plaque psoriasis submitted at 07/24/2017.

1. Please conduct post hoc reanalysis of efficacy endpoint (PGA, PASI75, PASI90) stratified by Dose (200 mg vs. 400 mg) and body weight low and high subgroups (e.g. BW < 90 kg vs. BW > 90 kg at 200 mg and 400 mg) in study CIMPASI-1, CIMPASI-2, CIMPACT and pooled studies.
2. Please conduct post hoc reanalysis of AE report stratified by Dose (200 mg vs. 400 mg) and body weight low and high subgroups (e.g. BW < 90 kg vs. BW > 90 kg at 200 mg and 400 mg) in study CIMPASI-1, CIMPASI-2, CIMPACT and pooled studies.
3. Please submit anti-drug antibodies (ADA) incident rate stratified by Dose (200 mg vs. 400 mg) and body weight low and high subgroups (e.g. BW < 90 kg vs. BW >90 kg at 200 mg and 400 mg) in study CIMPASI-1, CIMPASI-2, CIMPACT and pooled studies.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA J GOULD
05/24/2018

KENDALL A MARCUS
05/24/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Orig1s283

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

Date: May 8, 2018
To: File for STN: 125160/283 (SDN 1593, 07/24/2017)
From: Subramanian Muthukkumar Ph.D.
Through: Brian Janelsins, Ph.D.
Rachel Novak, Ph.D.
Applicant: UCB, Inc.
Product: Cimzia® (CDP870/certolizumab-pegol) – Recombinant humanized anti-TNF-α antibody Fab fragment conjugated to polyethylene glycol (200 mg/mL) lyophilized powder and solution for subcutaneous use.
Subject: STN 125160/283 Efficacy Supplement: Supplemental Biologic License Application (sBLA) for certolizumab pegol treatment of adults with moderate to severe chronic plaque psoriasis- Assessment of Biopharmaceutical Immunogenicity assay validation reports.

Action due date: May 24, 2018

Link: \\CDSESUB1\EVSPROD\BLA125160\125160.enx

Reviewer Recommendation: Approval. The immunogenicity assays are currently not adequate to assess the proposed patient population for the presence of binding and neutralizing anti-drug antibodies; however, two post marketing commitments will be conveyed to the sponsor to address the issues.

Note: *Reviewer comments are in italics. Tables and figures in the review memo are directly excerpted from the submission.*

SUBMISSION SUMMARY AND REVIEW:
An efficacy supplement was submitted to support the use of certolizumab-pegol (CDP870) for the treatment of adults with moderate to severe chronic plaque psoriasis. In support of the new indication, clinical data from efficacy, safety, immunogenicity, and PK/PD assessments were provided in the submission. No product quality changes were proposed in support of the new indication. The Environmental Assessment and the appropriateness of the immunogenicity assays were assessed from the product quality perspective. The immunogenicity assays, i.e., a double-antigen sandwich ELISA that detects the presence of binding anti-drug antibodies (ADAs) to CDP870 in human plasma samples and a HeLa cell bioassay that detects the presence of neutralizing ADAs (Nabs) to CDP870 in human plasma samples, were updated and re-validated in support of the new indication. The method validation reports for the binding antibody ((b) (4) Study Reports 8360-977 and 8360-977 Addendum 1) and neutralizing antibody ((b) (4) Study Report AR6633) assays that were used to analyze the clinical samples (Clinical Study PS0005) were provided. Because the immunogenicity assays, which are reviewed below, lack adequate sensitivity and are not tolerant to onboard levels of drug, these assays are not acceptable to assess the patient population for the presence of binding and neutralizing ADAs. Additionally, an assessment of ADAs binding to the PEG moiety of CDP870 in psoriasis patients was not provided. Because CDP870 is a pegylated product, the binding ADA assay used to test the clinical samples should be able to detect antibodies to both the PEG and Fab' fragment

moieties and generate data to allow for a determine of the incidences of ADA responses that are specific to the whole product and to each moiety of CDP870. Because of deficiencies with the binding and neutralizing antibody assays, as described above, a post-marketing commitment will be issued to the sponsor to improve the sensitivity of the assays and to assess the ability of the assays to detect ADAs against PEG.. Comments to be communicated to the applicant for consideration while improving the immunogenicity assays are placed at the end of the review as well.

(b) (4)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Orig1s283

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)

Epidemiology: ARIA Sufficiency Memo
Version: 2018-01-24

Date:	May 21, 2018
Reviewer/ Team Leader:	Patricia Bright, PhD, MSPH Division of Epidemiology I
Deputy Division Director:	Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	Active Risk Identification and Assessment (ARIA) Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Cimzia (Certolizumab Pegol)
Application Type/#:	BLA: 125160/S283
Applicant/Sponsor:	UCB
OSE RCM #:	2018-802

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Plaque psoriasis is a chronic inflammatory skin disease which may undergo intermittent improvements and relapses in susceptible individuals over the course of their lifetime. Although traditional systemic therapies for psoriasis are effective, there may be a loss of efficacy during long-term use or patients may experience adverse events related to specific treatments.

Cimzia (Certolizumab Pegol) 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.
- Treatment of adults with moderately to severely active rheumatoid arthritis.
- Treatment of adult patients with active psoriatic arthritis.
- Treatment of adults with active ankylosing spondylitis.

Supplement 283 for BLA 125160 is for the added indication of treating adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Cimzia contains a boxed warning for: Increased risk of serious infections (including TB) or sepsis, lymphoma, and other malignancies.

Warnings and precautions in the labeling include: serious infections, invasive fungal infections, cases of lymphoma and other malignancies, heart failure, anaphylaxis or serious allergic reactions, hepatitis B virus reactivation, demyelinating disease, cytopenia, and lupus-like syndrome.

1.2. Describe the Safety Concern – Pregnancy Risk

A Cimzia Pregnancy Exposure Registry has been established to follow pregnant women with a Cimzia approved indications (Crohn's Disease, Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis) who have or have not been treated with Cimzia during pregnancy to evaluate the possible effect of these diseases, and/or Cimzia on pregnancy outcomes including child development and growth up to five years of age. This prospective cohort study leverages the Organization of Teratology Information Services (OTIS) Registry to prospectively evaluate pregnancy outcomes. The Cimzia Pregnancy Exposure Registry was initiated in March 2012 with an enrollment goal of 300 participants. The proposed labeling refers pregnant women to this study [1].

In the context of the plaque psoriasis development program, nine pregnancies were reported in eight patients in Phase 2/3 trials [2]. One patient had two pregnancies. Three of the exposures occurred during the first trimester; patients underwent elective abortions. An additional exposure occurred during the first trimester with an outcome of missed spontaneous abortion (delayed miscarriage). Four pregnancies occurred with exposure at unknown gestation and with unknown outcomes. A pregnancy also occurred post-treatment exposure with an unknown outcome.

The Division of Pediatric and Maternal Health (DPMH) labeling review [3] for the Pregnancy and Lactation Labeling Rule (PLLR) stated that:

> "The applicant reviewed the literature on the association between psoriasis and adverse pregnancy outcomes, and concluded that available published data are inconsistent."
>
> "In addition, published data suggest that pregnant women with psoriasis have comorbidities such as obesity, smoking, and depression that may contribute to adverse pregnancy outcomes."
>
> "Based on available data that show inconsistent findings, the applicant has not proposed to include a statement on psoriasis associated maternal and embryo-fetal risk in labeling."

DPMH concurred with the sponsor's decision not to include a statement on psoriasis associated maternal and embryo-fetal risk in labeling and further clarified that:

> "Available data are not sufficient to inform the disease-associated risks of plaque psoriasis on pregnancy; therefore, no new statements will be added to labeling at the present time. Pregnancy and lactation labeling should remain unchanged from recently approved labeling."

The Cimzia labeling was modified and approved on March 20, 2018, to accommodate PLLR revisions. However, Section 8.1 of the labeling will not be modified further in response to the added indication of plaque psoriasis. The current labeling under Section 8.1 includes the following:

> **"USE IN SPECIFIC POPULATIONS**
>
> **8.1 Pregnancy**
>
> Pregnancy Exposure Registry
>
> There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to CIMZIA during pregnancy. For more information, healthcare providers or patients can contact:
>
> MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS). The OTIS AutoImmune Diseases Study at 1-877-311-8972 or visit http://mothertobaby.org/pregnancy-studies/
>
> Risk Summary
> Limited data from the ongoing pregnancy registry on use of CIMZIA in pregnant women are not sufficient to inform a risk of major birth defects or other adverse pregnancy outcomes. However, certolizumab pegol plasma concentrations obtained from two studies of CIMZIA use during the third trimester of pregnancy demonstrated that placental transfer of certolizumab pegol was negligible in most infants at birth, and low in other infants at birth (see Data). There are risks to the mother and fetus associated with active rheumatoid arthritis or Crohn's disease. The theoretical risks of administration of live or live-attenuated vaccines to the infants exposed in utero to CIMZIA should be weighed against the benefits of vaccinations (see Clinical Considerations). No adverse developmental effects were observed in animal reproduction studies during which pregnant rats were administered intravenously a rodent anti-murine TNFα pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol during organogenesis at up to 2.4 times the recommended human dose of 400 mg every four weeks.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Published data suggest that the risk of adverse pregnancy outcomes in women with rheumatoid arthritis or Crohn's disease is correlated with maternal disease activity and that active disease increases the risk of adverse pregnancy outcomes, including fetal loss, preterm delivery (before 37 weeks of gestation), low birth weight (<2500 g) and small for gestational age birth.

Fetal/Neonatal Adverse Reactions

Due to its inhibition of TNFα, CIMZIA administered during pregnancy could affect immune responses in the in utero-exposed newborn and infant. The clinical significance of BLQ or low levels is unknown for in utero-exposed infants. Additional data available from one exposed infant suggest that CIMZIA may be eliminated at a slower rate in infants than in adults (see Data). The safety of administering live or live-attenuated vaccines in exposed infants is unknown.

Data

Human Data

A limited number of pregnancies have been reported in the ongoing pregnancy exposure registry. Due to the small number of CIMZIA-exposed pregnancies with known outcomes (n=58), no meaningful comparisons between the exposed group and control groups may be conducted to determine an association with CIMZIA and major birth defects or adverse pregnancy outcomes.

A multicenter clinical study was conducted in 16 women treated with CIMZIA at a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks during pregnancy for rheumatological diseases or Crohn's disease. The last dose of CIMZIA was given on average 11 days prior to delivery (range 1-27 days). Certolizumab pegol plasma concentrations measured in the mothers at delivery infants using an assay that can measure certolizumab pegol concentrations at or above 0.032 mcg/mL. Certolizumab pegol plasma concentrations measured in the mothers at delivery (range: 4.96 – 49.4 mcg/ml) were consistent with non-pregnant women's plasma concentrations in Study RA-1 [see Clinical Studies (14.2)]. Certolizumab pegol plasma concentrations were not measurable in 13 out of 15 infants at birth. The concentration of certolizumab pegol in one infant was 0.042 mcg/ml at birth (0.09% infant/mother plasma ratio). In a second infant, delivered by emergency Caesarean section, the concentration was 0.485 mcg/mL (infant/mother plasma ratio of 4.49%). At Week 4 and Week 8, all 15 infants had no measurable concentrations. Among 16 exposed infants, one serious adverse event was reported in a neonate who was treated empirically with intravenous antibiotics due to an increased white blood cell count; blood cultures were negative. The certolizumab pegol plasma concentrations for this infant were not measurable at birth, Week 4, or Week 8.

In another clinical study conducted in 10 pregnant women with Crohn´s disease treated with CIMZIA (400 mg every 4 weeks for every mother), certolizumab pegol concentrations were measured in maternal blood as well as in cord and infant blood at the day of birth with an assay that can measure concentrations at or above 0.41 mcg/mL. The last dose of CIMZIA

was given on average 19 days prior to delivery (range 5-42 days). Plasma certolizumab pegol concentrations ranged from not measurable to 1.66 mcg/mL in cord blood and 1.58 mcg/mL in infant blood; and ranged from 1.87–59.57 mcg/mL in maternal blood. Plasma certolizumab pegol concentrations were lower (by at least 75%) in the infants than in mothers suggesting low placental transfer of certolizumab pegol. In one infant, the plasma certolizumab pegol concentration declined from 1.02 to 0.84 mcg /mL over 4 weeks suggesting that CIMZIA may be eliminated at a slower rate in infants than adults.

Animal Data
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. Animal reproduction studies have been performed in rats during organogenesis at intravenous doses up to 100 mg/kg (about 2.4 times the recommended human dose of 400 mg, based on the surface area) and have revealed no evidence of harm to the fetus due to cTN3 PF."

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☒ Electronic database study without chart review
☐ Other, please specify:

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population and Outcomes: ARIA is insufficient to identify the study population (babies that experienced in utero exposure or postpartum exposure through lactation) because the mother and baby records are not currently linked in Sentinel. Thus, the exposure corresponding to the mother and potential outcomes corresponding to the infant cannot be connected. This lack of linkage between mother and baby records renders ARIA insufficient for both the study population and outcome identification.

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

We did not formally assess the other parameters given that the mother-infant linkage is not currently available in ARIA.

2.5. Please include the proposed PMR language in the approval letter.

The following language (still in draft form) has been proposed for PMRs related to pregnancy outcomes:

A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to certolizumab pegol during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, will be assessed through at least the first year of life. You may expand a current prospective registry to include women who are exposed

to certolizumab pegol for the treatment of plaque psoriasis.

And

Conduct a retrospective cohort study using claims or electronic medical record data or a case control study to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths, and infant infections in women exposed to certolizumab pegol during pregnancy compared to an unexposed control population.

The finalized PMR language will be issued upon approval.

[1] https://clinicaltrials.gov/ct2/show/NCT01797224, Accessed May 14, 2018.
[2] BLA Multi-disciplinary Review and Evaluation – BLA: 125160/S283761067, Cimzia (Certolizumab Pegol), Accessed May 15, 2018, DARRTS Reference ID: Pending.
[3] Sahin, Leyla, Division of Pediatric and Maternal Health, Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review, BLA 125160/S-283, dated March 26, 2018, Reference ID: 4239710.

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/s/

PATRICIA L BRIGHT
05/21/2018

SUKHMINDER K SANDHU
05/21/2018

JUDITH W ZANDER
05/21/2018

MICHAEL D NGUYEN
05/21/2018

ROBERT BALL
05/21/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 11, 2018
To:	Kendall Marcus, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jina Kwak, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	CIMZIA (certolizumab pegol)
Dosage Form and Route:	For injection or injection, for subcutaneous use
Application Type/Number:	BLA 125160
Supplement Number:	S-283
Applicant:	UCB, Inc.

1 INTRODUCTION

On July 24, 2017, UCB Inc., submitted for the Agency's review a Supplemental Biologics Application (sBLA) for CIMZIA (certolizumab pegol) seeking the approval to market CIMZIA (certolizumab pegol) injection or for injection, for subcutaneous use, for the treatment of adults with moderate to severe chronic plaque psoriasis who are eligible for systemic therapy or phototherapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on October 12, 2017, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for CIMZIA (certolizumab pegol) injection or for injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft CIMZIA (certolizumab pegol) MG received on July 24, 2017, and received by DMPP and OPDP on April 4, 2018.
- Draft CIMZIA (certolizumab pegol) Prescribing Information (PI) received on July 24, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 4, 2018.

3 REVIEW METHODS

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%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
04/11/2018

JINA KWAK
04/11/2018

LASHAWN M GRIFFITHS
04/11/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: April 6, 2018

To: Melissa Reyes, MD, Medical Officer
Division of Dermatology and Dental Products (DDDP)

Barbara Gould, Chief Project Management Staff
DDDP

From: Jina Kwak, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, PharmD, Team Leader, OPDP

Subject: **BLA 125160/S-283**
OPDP labeling comments for CIMZIA (certolizumab pegol) for injection, for subcutaneous use

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In response to DDDP consult request dated October 12, 2017, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for CIMZIA (certolizumab pegol) for injection, for subcutaneous use. This supplement includes the new indication for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDDP on April 3, 2018 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Jina Kwak: 301-796-4809; Jina.Kwak@fda.hhs.gov

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/s/

JINA KWAK
04/06/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pregnancy and Lactation Labeling Review

Date: 3-26-2018

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S.
Team Leader, Maternal Health
Division of Pediatric and Maternal Health

To: Division of Dermatology and Dental Products

Drug: Cimzia (certolizumab pegol) for subcutaneous injection; BLA125160/S-283

Approved Indications:

- 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
- Treatment of adults with moderately to severely active rheumatoid arthritis
- Treatment of adult patients with active psoriatic arthritis
- Treatment of adults with active ankylosing spondylitis.

Proposed Indication: Treatment of adults with moderate to severe chronic plaque psoriasis who are eligible for systemic therapy or phototherapy

Subject: Pregnancy and Lactation Labeling Review as part of efficacy supplement

Applicant: UCB

Materials Reviewed:
- Applicant's submission
- Approved Cimzia labeling (03-20-2018)
- Literature review

Consult Question: Please assist with updating Pregnancy and Lactation Labeling

INTRODUCTION AND BACKGROUND

The applicant submitted an efficacy supplement on July 24, 2017, for a new proposed indication for the treatment of adults with moderate to severe chronic plaque psoriasis who are eligible for systemic therapy or phototherapy. The Division of Dermatology and Dental Products (DDDP) consulted the Division of Pediatric and Maternal Health (DPMH) on September 27, 2017 to assist with the Pregnancy and Lactation subsections of labeling.

DPMH was concurrently involved with revising the Cimzia Pregnancy and Lactation subsections of labeling for a Prior Approval Labeling Supplement submitted to the Division of Gastroenterology and Inborn Errors Products (DGIEP). On March 20, 2018, DGIEP approved pregnancy and lactation labeling revisions that included the addition of pharmacokinetic data in pregnant women and lactation data, based on studies that were conducted voluntarily by the applicant.[1] The reader is referred to the DPMH labeling review for a review of data from the pharmacokinetic and lactation studies, the Organization of Teratology Information Specialists (OTIS) Pregnancy Registry, the applicant's safety database, and the medical literature.[2] The reader is referred to the Clinical Pharmacology review by Dr. Anand Balakrishnan for a review of the pharmacokinetic and lactation study reports.[3]

This review provides a review of additional information in support of the pregnancy and lactation labeling for the current efficacy supplement.

REVIEW

Plaque Psoriasis Development Program

Seven pregnancies occurred during the development program for plaque psoriasis with the following outcomes: 1 healthy newborn, 3 elective terminations, and 3 pending.

Applicant conclusion

The applicant concluded that these data do not indicate any safety concerns.

Reviewer comment
DPMH concurs.

[1] see Approval Letter in DARRTS dated 3-20-2018

[2] see review in DARRTS By Leyla Sahin, MD, dated 9-20-2017

[3] see review in DARRTS dated 12-21-2017

Plaque Psoriasis and Pregnancy
The applicant reviewed the literature on the association between psoriasis and adverse pregnancy outcomes, and concluded that available published data are inconsistent. See Table 1 in the Appendix for a summary of published studies that assessed the association between psoriasis and adverse pregnancy outcomes, including additional publications identified by this reviewer.

In addition, published data suggest that pregnant women with psoriasis have comorbidities such as obesity, smoking, and depression that may contribute to adverse pregnancy outcomes.[4]

Based on available data that show inconsistent findings, the applicant has not proposed to include a statement on psoriasis associated maternal and embryo-fetal risk in labeling.

Reviewer comments
DPMH concurs.

DISCUSSION AND CONCLUSION

Available data are not sufficient to inform the disease-associated risks of plaque psoriasis on pregnancy; therefore, no new statements will be added to labeling at the present time. Pregnancy and lactation labeling should remain unchanged from recently approved labeling.

DPMH LABELING RECOMMENDATIONS

DPMH recommendations reflect labeling approved on 3-20-2018, and are below.
See final labeling for all of the labeling revisions negotiated with the applicant.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to CIMZIA during pregnancy. For more information, healthcare providers or patients can contact:

MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS). The OTIS AutoImmune Diseases Study at 1-877-311-8972 or visit http://mothertobaby.org/pregnancy-studies/

Risk Summary
Limited data from the ongoing pregnancy registry on use of CIMZIA in pregnant women are not sufficient to inform a risk of major birth defects or other adverse pregnancy outcomes. However, certolizumab pegol plasma concentrations obtained from two studies of CIMZIA use during the third trimester of pregnancy demonstrated that placental transfer of certolizumab pegol was negligible in most infants at birth, and low in other infants at birth *(see Data)*. There are risks to the mother and fetus associated with active rheumatoid arthritis or Crohn's disease. The

[4] Bandoli G1, Johnson DL, Jones KL, Lopez Jiminez J, Salas E, Mirrasoul N, et al. Potentially modifiable risk factors for adverse pregnancy outcomes in women with psoriasis. Br J Dermatol. 2010; 163 (2):334-9.

theoretical risks of administration of live or live-attenuated vaccines to the infants exposed *in utero* to CIMZIA should be weighed against the benefits of vaccinations *(see Clinical Considerations)*. No adverse developmental effects were observed in animal reproduction studies during which pregnant rats were administered intravenously a rodent anti-murine TNFα pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol during organogenesis at up to 2.4 times the recommended human dose of 400 mg every four weeks.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Published data suggest that the risk of adverse pregnancy outcomes in women with rheumatoid arthritis or Crohn's disease is correlated with maternal disease activity and that active disease increases the risk of adverse pregnancy outcomes, including fetal loss, preterm delivery (before 37 weeks of gestation), low birth weight (<2500 g) and small for gestational age birth.

Fetal/Neonatal Adverse Reactions

Due to its inhibition of TNFα, CIMZIA administered during pregnancy could affect immune responses in the in utero-exposed newborn and infant. The clinical significance of BLQ or low levels is unknown for in utero-exposed infants. Additional data available from one exposed infant suggest that CIMZIA may be eliminated at a slower rate in infants than in adults *(see Data)*. The safety of administering live or live-attenuated vaccines in exposed infants is unknown.

Data

Human Data

A limited number of pregnancies have been reported in the ongoing pregnancy exposure registry. Due to the small number of CIMZIA-exposed pregnancies with known outcomes (n=58), no meaningful comparisons between the exposed group and control groups may be conducted to determine an association with CIMZIA and major birth defects or adverse pregnancy outcomes.

A multicenter clinical study was conducted in 16 women treated with CIMZIA at a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks (b) (4) for rheumatological diseases or Crohn's disease. The last dose of CIMZIA was given on average 11 days prior to delivery (range 1-27 days). Certolizumab pegol plasma concentrations (b) (4) using an assay that can measure certolizumab pegol concentrations at or above 0.032 mcg/mL. Certolizumab pegol plasma concentrations measured in the mothers at delivery (range: 4.96 – 49.4 mcg/ml) were consistent with non-pregnant women's plasma concentrations in Study RA-1 *[see Clinical Studies (14.2)]*. Certolizumab pegol plasma concentrations were not measurable in 13 out of 15 infants at birth. The concentration of certolizumab pegol in one infant was 0.042 mcg/ml at birth (0.09% infant/mother plasma ratio). In a second infant, delivered by emergency Caesarean section, the concentration was 0.485

mcg/mL (infant/mother plasma ratio of 4.49%). At Week 4 and Week 8, all 15 infants had no measurable concentrations. Among 16 exposed infants, one serious adverse event was reported in a neonate who was treated empirically with intravenous antibiotics due to an increased white blood cell count; blood cultures were negative. The certolizumab pegol plasma concentrations for this infant were not measurable at birth, Week 4, or Week 8.

In another clinical study conducted in 10 pregnant women with Crohn´s disease treated with CIMZIA (400 mg every 4 weeks for every mother), certolizumab pegol concentrations were measured in maternal blood as well as in cord and infant blood at the day of birth with an assay that can measure concentrations at or above 0.41 mcg/mL. The last dose of CIMZIA was given on average 19 days prior to delivery (range 5-42 days). Plasma certolizumab pegol concentrations ranged from not measurable to 1.66 mcg/mL in cord blood and 1.58 mcg/mL in infant blood; and ranged from 1.87–59.57 mcg/mL in maternal blood. Plasma certolizumab pegol concentrations were lower (by at least 75%) in the infants than in mothers suggesting low placental transfer of certolizumab pegol. In one infant, the plasma certolizumab pegol concentration declined from 1.02 to 0.84 mcg /mL over 4 weeks suggesting that CIMZIA may be eliminated at a slower rate in infants than adults.

Animal Data
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. Animal reproduction studies have been performed in rats during organogenesis at intravenous doses up to 100 mg/kg (about 2.4 times the recommended human dose of 400 mg, based on the surface area) and have revealed no evidence of harm to the fetus due to cTN3 PF.

8.2 Lactation
Risk Summary
In a multicenter clinical study of 17 lactating women treated with CIMZIA at 200 mg every 2 weeks or 400 mg every 4 weeks, minimal certolizumab pegol levels were observed in breast milk. No serious adverse reactions were noted in the 17 infants in the study. There are no data on the effects on milk production. In a separate study, certolizumab pegol concentrations were not detected in the plasma of 9 breastfed infants at week 4 postpartum *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Cimzia and any potential adverse effects on the breastfed infant from Cimzia or from the underlying maternal condition.

Data
A multicenter clinical study designed to evaluate breast milk was conducted in 17 lactating women who were at least 6 weeks post-partum and had received at least 3 consecutive doses of Cimzia 200 mg every 2 weeks or 400 mg every 4 weeks for rheumatological disease or Crohn's disease. The effects of certolizumab pegol on milk production were not studied. The concentration of certolizumab pegol in breast milk was not measurable in 77 (56%) of the 137 samples taken over the dosing periods using an assay that can measure certolizumab pegol concentrations at or above was 0.032 mcg/mL. The median of the estimated average daily infant doses was 0.0035 mg/kg/day (range: 0 - 0.01 mg/kg/day). The percentage of the maternal dose (200 mg CIMZIA dosed once every 2 weeks), that reaches an infant ranged from 0.56% to

4.25% based on samples with measurable certolizumab pegol concentration. No serious adverse reactions were noted in the 17 (b) (4) in the study.

In a separate study, plasma certolizumab pegol levels were collected 4 weeks after birth in 9 breastfed infants whose mothers had been currently taking CIMZIA(regardless of being exclusively breastfed or not). Certolizumab pegol in infant plasma was not measurable i.e., below 0.032 mcg/mL.

APPENDIX

Table 1 Summary of Published Studies on Psoriasis and Pregnancy Outcomes∗

Study	Number (pregnant women with psoriasis)	Comparator number	Findings	Comments
Carman 2017[5] U.S. Retrospective cohort study based on claims data	81 with psoriasis, exposed to a treatment other than etanercept; 1,349 with psoriasis, unexposed	405 general population	No difference in rate of major malformations or spontaneous abortion among all 3 groups	No statistical analysis was performed
Harder 2014[6] Denmark ∗∗ Retrospective cohort study based on national data	2,553	85, 139 general population	No increased risk of spontaneous abortion or stillbirth	No other outcomes were assessed
Lima 2012[7] U.S. ∗∗ Retrospective cohort study based on claims data	122	290 general population	Increased risk of preterm birth and low birth weight (less than 2,500 g) as a composite outcome, but no increased risk when assessed separately	Conflicting findings preclude interpretation; clinical relevance of composite outcome not clear

[5] Carman WJ, Accortt NA, Anthony MS, Iles J, Enger C. Pregnancy and infant outcomes including major congenital malformations among women with chronic inflammatory arthritis or psoriasis, with and without etanercept use. Pharmacoepidemiol Drug Saf. 2017; 26 (9):1109-1118.

[6] Harder E, Anderson AM N, Jorgenson MK et al. No increased risk of fetal death or prolonged time to pregnancy in women with psoriasis. J Investigative Derm 2014: 134:1747-1749.

[7] Lima XT, Janakiraman V, Hughes MD, Kimball A. The Impact of psoriasis on pregnancy outcomes. J Investigative Derm 2012: 134:85-91.

Study	Number (pregnant women with psoriasis)	Comparator number	Findings	Comments
Yang 2011[8] Taiwan ∗∗ Retrospective cohort study based on national claims data	818 with mild psoriasis (no treatment) 645 with severe psoriasis (systemic therapy or phototherapy)	11,704 general population	Increased risk of low birth weight in women with severe psoriasis OR 1.4, 95% CI 1.04-1.89; No increased risk for small for gestational age, preterm birth, or pre-eclampsia/eclampsia	Low birth weight in the absence of small for gestational age and preterm birth is difficult to interpret; no other outcomes were assessed

∗Only peer reviewed manuscripts were reviewed; abstracts were not included.
∗∗ Publication identified by this reviewer

[8] Yang YM, Chen CS, Chen YC, Lin HC. Psoriasis and pregnancy outcomes. J Am Acad Dermatol 2011; 64:71-7.

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/s/

LEYLA SAHIN
03/26/2018

TAMARA N JOHNSON
03/27/2018