CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125160Orig1s237

Trade Name:	CIMZIA
Generic or Proper Name:	(certolizumab pegol)
Sponsor:	Neurocrine Bioscience Inc.
Approval Date:	March 28, 2019
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 • 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 • Treatment of adults with active non-radiographic axial spondylarthritis with objective signs of inflammation • Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

CENTER FOR DRUG EVALUATION AND RESEARCH

125160Origs0237

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Orig1s237

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125160/S-237

SUPPLEMENT APPROVAL

UCB, Inc.
1950 Lake Park Drive
Building 2100
Smyrna, GA 30080

Attention: Jennifer King
Associate Director, Regulatory Affairs

Dear Ms. King:

Please refer to your Supplemental Biologics License Application (sBLA) dated December 14, 2012, received December 17, 2012, and your amendments, submitted under section 351(a) of the Public Health Service Act for Cimzia (certolizumab pegol) Lyophilized Powder and Solution for Subcutaneous Use, 200 mg/mL.

We acknowledge receipt of your amendment dated September 28, 2018, which constituted a complete response to our October 17, 2013, action letter.

This Prior Approval supplemental biologics application proposes a new indication for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation.

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.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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 h tp://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the Prescribing Information, and 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 h tp://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 Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 125160/S-237**." Approval of this submission by FDA is not required before the labeling is used.

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 this application because necessary studies are impossible or highly impracticable as this condition rarely occurs in pediatrics.

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 Nina Ton, Senior Regulatory Project Manager, at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD
Acting Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NIKOLAY P NIKOLOV
03/28/2019 01:14:41 PM
Signed under the authority delegated by Dr. Sally Seymour, Acting Division Director, DPARP.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Origs237

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125160/237

COMPLETE RESPONSE

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

Attention: Sandra V. Bonsall, RAC
Director, Regulatory Affairs

Dear Ms. Bonsall:

Please refer to your Supplemental Biologics License Application (sBLA) dated December 14, 2012, received December 17, 2012, submitted under section 351(a) of the Public Health Service Act for Cimzia (certolizumab pegol).

We acknowledge receipt of your amendment dated September 26, 2013.

This Prior Approval efficacy supplement to your biologics license application proposes an indication for the treatment of adults with axial spondyloarthritis.

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

CLINICAL

1. The submitted data from study AS001 are inadequate to support approval of Cimzia at a dose of 200 mg subcutaneously every other week or 400 mg subcutaneously every four weeks for the treatment of patients with axial spondyloarthritis. The populations proposed for a broader axial spondyloarthritis indication are subgroups of the overall study population who have not been studied adequately to demonstrate efficacy and safety.

2. To support approval of Cimzia for a broader axial spondyloarthritis indication, provide efficacy and safety data from at least one controlled 12-month trial in patients who are clearly identified to have non-radiographic axial spondyloarthritis. Exclude patients with ankylosing spondylitis from the study. Ensure adequate representation of patients in each of these groups: positive MRI findings at the sacroiliac joints, elevated CRP at baseline, and both positive MRI findings at the sacroiliac joints and elevated CRP at baseline. Consider other factors that may impact the effect of treatment, such as duration of disease, and prior use of therapy. Develop and submit plans for risk mitigation and safe use of Cimzia in the targeted population.

LABELING

3. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). You are advised to contact the Division of Pulmonary, Allergy, and Rheumatology Products regarding the extent and format of your safety update prior to responding to this letter.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Nina Ton, Regulatory Project Manager, at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

BADRUL A CHOWDHURY
10/17/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Origs237

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)	03/2019
Indications and Usage (1.6)	05/2018
Dosage and Administration (2.5)	03/2019
Dosage and Administration (2.6)	05/2018
Dosage and Administration (2.7)	02/2019
Contraindications (4)	05/2018
Warnings and Precautions (5.4)	02/2019

----------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 active non-radiographic axial spondyloarthritis with objective signs of inflammation (1.5)
- Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (1.6)

----------DOSAGE AND ADMINISTRATION----------

CIMZIA is administered by subcutaneous injection. The recommended 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.

Non-radiographic Axial Spondyloarthritis (2.5)

- 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 (2.6, 14.6)

- 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: CIMZIA should not be initiated in patients with an active infection. Monitor for infection during and after treatment; discontinue if a serious infection develops. If invasive fungal infection develops in patients who reside or travel to regions where mycoses are endemic, consider empiric antifungal therapy. (5.1)
- Malignancies: Cases of lymphoma and other malignancies have been observed among patients receiving TNF blockers, including CIMZIA. (5.2)
- Heart Failure: Monitor patients for new onset or worsening congestive heart failure. (5.3)
- Hypersensitivity Reactions: Discontinue CIMZIA and institute appropriate therapy if anaphylaxis or other serious hypersensitivity reactions 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)
- Neurologic Reactions: Exacerbation or new onset demyelinating disease may occur; use caution in patients with pre-existing or recent-onset demyelinating disorders. (5.6)
- Hematological Reactions (including leukopenia, pancytopenia and thrombocytopenia): Use with caution in patients who have ongoing, or a history of, significant hematologic abnormalities. Advise patients to seek immediate medical attention if symptoms develop; consider discontinuing CIMZIA in patients with confirmed abnormalities. (5.7)
- Use with Anakinra, Abatacept, Rituximab and Natalizumab: Increased risk of serious infections; concomitant use is not recommended. (5.8, 7.1)
- Autoimmunity: Discontinue CIMZIA if lupus-like syndrome develops. (5.9)
- Live vaccines: Avoid use with CIMZIA (5.10, 7.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥7%): 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----------

- Laboratory Tests: May cause erroneously elevated aPTT results. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2019

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 Non-radiographic Axial Spondyloarthritis

CIMZIA is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation *[see Clinical Studies (14.5)]*.

1.6 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 (14.6)]*

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 Non-radiographic Axial Spondyloarthritis

The recommended dose of CIMZIA for adult patients with non-radiographic axial spondyloarthritis 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.

2.6 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 (14.6)]*.

2.7 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. If refrigerated, 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.

2.8 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.

- If refrigerated, remove the prefilled syringe from the carton and let it warm to room temperature.
- Inspect the liquid in the prefilled syringe. It should be clear and colorless to yellow and free from particulates. Discard the syringe if cloudy, discolored or contains particulates.
- Suitable sites for injection include the thigh or abdomen at least 2 inches away from the navel.

Inject at least 1 inch from the previous site.
- Do not inject into areas where the skin is tender, bruised, red or hard, or where there are scars or stretch marks.

The needle shield inside the removable cap of the CIMZIA prefilled syringe contains a derivative of natural rubber latex which may cause allergic reactions and should be handled with caution by latex-sensitive individuals *[see Warnings and Precautions (5.4)]*.

2.9 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.

2.10 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 white to off-white 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, anaphylaxis, 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 blockers, 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, anaphylaxis, 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)]*.

The needle shield inside the removable cap of the CIMZIA prefilled syringe contains a derivative of natural rubber latex which may cause an allergic reaction in individuals sensitive to latex.

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.

Non-radiographic Axial Spondyloarthritis Clinical Study

CIMZIA has been studied in 317 patients with non-radiographic axial spondyloarthritis (nr-axSpA-1). The safety profile for patients with nr-axSpA treated with CIMZIA was similar to the safety profile seen in patients with RA and previous experience with CIMZIA.

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)]*.

Hypersensitivity Reactions

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

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.

Reference ID: 4410921

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

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to certolizumab pegol in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

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.

A more sensitive and drug tolerant electrochemiluminesence (ECL)-based bridging assay was used for the first time in the nr-axSpA-1 study, resulting in a greater proportion of samples having measurable antibodies to certolizumab pegol and thus a greater incidence of patients being classed as antibody positive. In the placebo-controlled trial in patients with non-radiographic axial spondyloarthritis, after up to 52 weeks of treatment, the overall incidence of patients who were antibody positive to certolizumab pegol was 97% (248/255 patients). Of these antibody positive patients, higher titers were associated with reduced certolizumab pegol plasma levels.

The data above reflect the percentage of patients whose test results were considered positive for antibodies to certolizumab pegol in an ELISA or ECL-based bridging assay, and are highly dependent on the sensitivity and specificity of the assay.

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

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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.

Specific 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. When assessed using the previous ELISA method, the presence of anti-certolizumab antibodies was associated with a $\geq$ 3 to 4 fold increase in clearance.

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

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Racial or Ethnic Groups: A specific clinical study showed no difference in pharmacokinetics between Caucasian and Japanese subjects.

Male and Female Patients: Pharmacokinetics of certolizumab pegol was similar in male and female subjects.

Patients with 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.

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

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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.

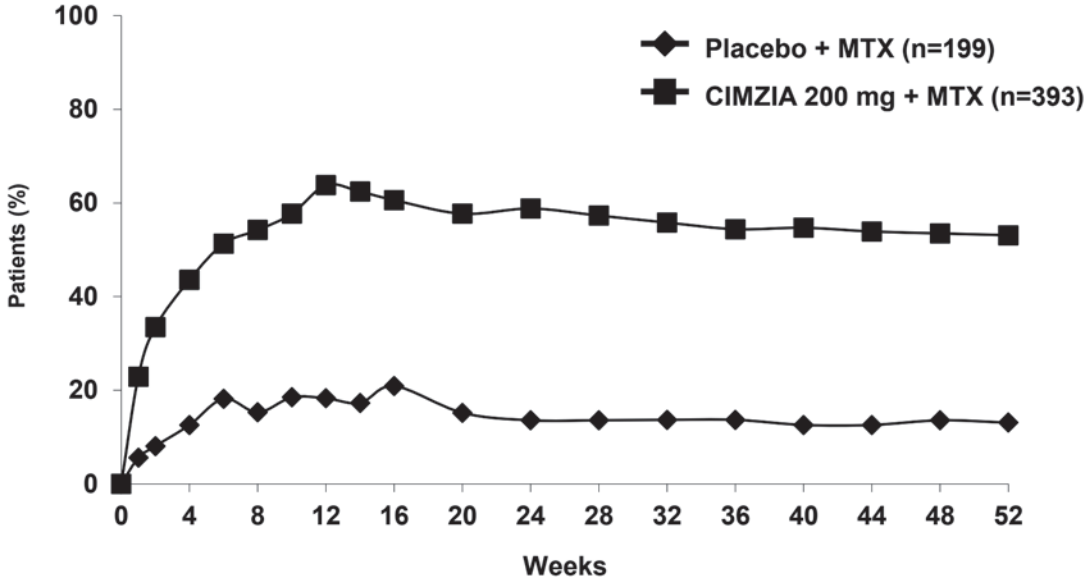
Table 6: Components of ACR Response in Studies RA-I and RA-IV

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 ≤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

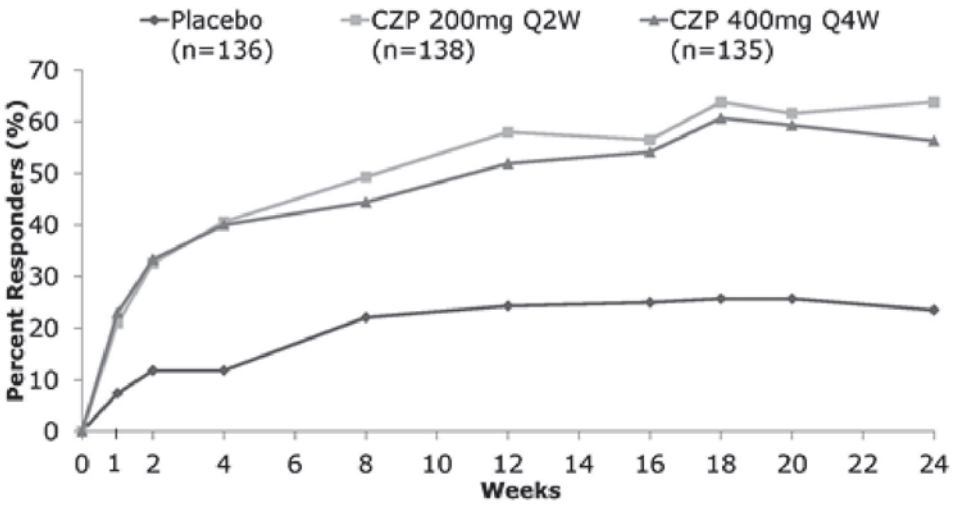
Parameter	Placebo[c] N=136		CIMZIA[a] 200 mg Q2W N=138		CIMZIA[b] 400 mg Q4W N=135	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
Number of tender joints (0-68)[d]	20	17	22	11	20	11
Number of swollen joints (0-66)[d]	10	9	11	4	11	5
Physician global assessment[d, e]	59	44	57	25	58	29
Patient global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

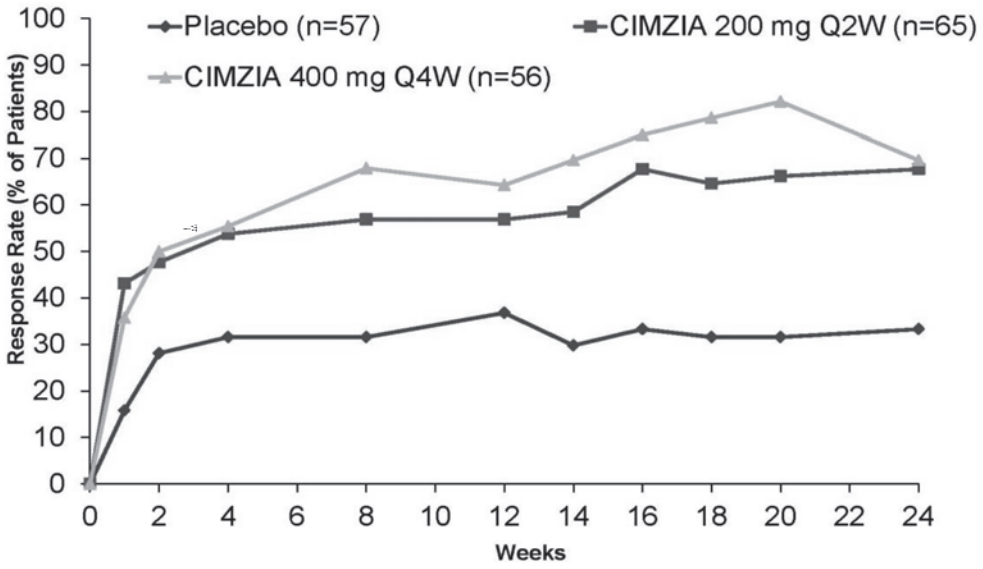
	Placebo N=57		**CIMZIA[(a)] 200 mg every 2 weeks N=65**		**CIMZIA[(b)] 400 mg every 4 weeks N=56**	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
ASAS20 response criteria						

-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 Non-radiographic Axial Spondyloarthritis

The efficacy and safety of CIMZIA were assessed in a multicenter, randomized, double-blind, placebo-controlled study (nr-axSpA-1) (NCT02552212) in 317 subjects ≥18 years of age with adult-onset active axial spondyloarthritis for at least 12 months. Patients must have had objective signs of inflammation indicated by C-reactive protein (CRP) levels above the upper limit of normal and/or sacroiliitis on magnetic resonance imaging (MRI), indicative of inflammatory disease [positive CRP (> ULN) and/or positive MRI], but without definitive radiographic evidence of structural damage on sacroiliac joints. 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 two NSAIDs. Patients were treated with a loading dose of CIMZIA 400 mg at Weeks 0, 2 and 4 or placebo followed by 200 mg of CIMZIA every 2 weeks or placebo. Utilization and dose adjustment of concomitant medications (including NSAIDs, DMARDs, corticosteroids, opioids) were permitted at any time. Patients were allowed to transition to use of open-label CIMZIA at any time at the discretion of the investigator. However, no patients transitioned before Week 12. The primary endpoint was the proportion of patients achieving an Ankylosing Spondylitis Disease Activity Score-Major Improvement (ASDAS-MI) response at Week 52. The ASDAS is a composite weighted scoring system that assesses disease activity, including patient-reported outcomes and CRP levels. A response in ASDAS-Major Improvement (MI) is indicated by a change from baseline of ≥2.0 in the ASDAS and/or reaching the lowest possible ASDAS value.

Clinical Response

In study nr-axSpA-1, at Week 52, a greater proportion of nr-axSpA patients treated with CIMZIA had ASDAS-MI response compared to patients treated with placebo. At both Weeks 12 and 52, ASAS40 responses were greater for patients treated with CIMZIA compared to patients treated with placebo (Table 12). The components of the ASDAS-MI and ASAS response criteria are shown in Table 13.

Table 12: Clinical Responses in nr-axSpA patients at Weeks 12 and 52 in study nr-axSpA-1

Parameters	Placebo N=158	CIMZIA[(a)] 200 mg every 2 weeks N=159	CIMZIA 200 mg versus Placebo Odds ratio (95% CI)
ASDAS-MI			
Week 52	7%	47%	15.2 (7.3 , 31.6)
ASAS-40			
Week 12	11%	48%	7.4 (4.1, 13.4)
Week 52	16%	57%	7.4 (4.3, 12.6)

[(a)]CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2, and 4
All percents reflect the proportion of patients who were responders and remained in the study and on randomized treatment in the full analysis set. Patients who initiated open-label CIMZIA, or discontinued randomized treatment and remained in the study, or were missing Week 52 visit data were imputed as non-responders.

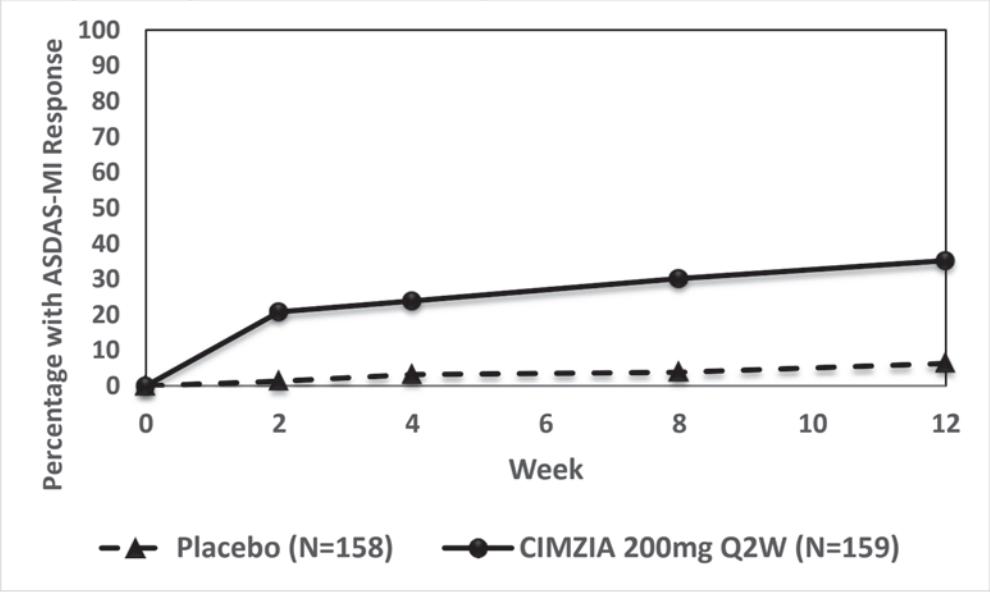
Table 13: Components of the ASDAS-MI and ASAS response criteria and other measures of disease activity in nr-axSpA patients at baseline, and at Week 12 in study nr-axSpA-1

	Placebo N=158		CIMZIA [(a)] 200 mg every 2 weeks N=159	
	Baseline (SD)	Week 12 (SD)	Baseline (SD)	Week 12 (SD)
Total Spinal Pain (0-10)	6.9 (1.8)	6.0 (2.3)	7.0 (1.9)	3.9 (2.6)
Patient Global Assessment of Disease Activity (0-10)	6.7 (2.0)	5.9 (2.4)	6.8 (1.9)	3.8 (2.6)
C-Reactive Protein (mg/L)	15.8 (17.7)	13.2 (17.2)	15.8 (17.8)	6.7 (15.1)
BASDAI (0-10)[(b)]	6.8 (1.3)	5.7 (2.1)	6.9 (1.4)	3.9 (2.2)
- Back Pain	7.4 (1.3)	6.2 (2.1)	7.4 (1.4)	4.1 (2.5)
- Peripheral pain and swelling (0-10)	6.2 (2.2)	5.3 (2.5)	6.3 (2.3)	3.7 (2.4)
- Inflammation[(c)]	6.7 (1.8)	5.5 (2.4)	6.9 (1.8)	3.6 (2.4)
BASFI (0-10)[(d)]	5.4 (2.2)	4.9 (2.4)	5.4 (2.1)	3.2 (2.3)
BASMI [(e)]	2.8 (1.4)	2.7 (1.4)	3.0 (1.3)	2.6 (1.4)

[(a)]CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2, and 4
[(b)]BASDAI is Bath Ankylosing Spondylitis Disease Activity Index
[(c)]The average of BASDAI question 5 and 6 concerning morning stiffness intensity and duration.
[(d)]BASFI is Bath Ankylosing Spondylitis Functional Index
[(e)]BASMI is Bath Ankylosing Spondylitis Metrology Index
Mean and standard deviation in parenthesis were presented based on full analysis set.

The percentage of nr-axSpA patients achieving ASDAS-MI response by visit for study nr-axSpA-1 is shown in Figure 4.

Figure 4: Study nr-axSpA-1: ASDAS-MI response over 12 weeks *



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

In study AS-1, at Week 12, patients with nr-axSpA treated with CIMZIA 200 mg every 2 weeks and CIMZIA 400 mg every 4 weeks had an ASAS 20 response of 42% and 47%, respectively, compared to 20% of patients treated with placebo. The ASAS 40 response in patients treated with CIMZIA 200 mg every 2 weeks and 400 mg every 4 weeks was 30% and 37%, respectively, compared to 11% of patients treated with placebo at Week 12 *(see Section 14.4)*.

Other Health Related Outcomes

In study nr-axSpA-1, at Week 12, patients treated with CIMZIA achieved significantly greater improvement from baseline in the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score compared to patients treated with placebo.

14.6 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 15 presents the efficacy results of PS-1, PS-2, and PS-3 at Week 16.

Reference ID: 4410921

Table 15: 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.

Unopened CIMZIA vials may also be stored at room temperature up to a maximum of 25°C (77°F) for 6 months, but not exceeding the original expiration date. If stored at room temperature, do not place back in refrigerator and write the new expiration date on the carton in the space provided.

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-dose prefilled glass syringes with a fixed 25 ½ gauge thin-wall needle, each containing 200 mg (1 mL) of CIMZIA. The needle shield inside the removable cap of the CIMZIA prefilled syringe contains a derivative of natural rubber latex which may cause allergic reactions and should be handled with caution by latex-sensitive individuals *[see Warnings and Precautions (5.4)]*.

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 °F (25 °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 and Instructions for Use)

Risk of Serious Infections

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.

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 *[see Warnings and Precautions (5.1, 5.5)]*.

Malignancies

Counsel patients about the possible risk of lymphoma and other malignancies while receiving CIMZIA *[see Warnings and Precautions (5.2)]*.

Other Medical Conditions

Advise patients to report any signs of new or worsening medical conditions such as heart disease, neurological disease, or autoimmune disorders *[see Warnings and Precautions (5.3, 5.6, 5.9)*. Advise patients to report promptly any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever *[see Warnings and Precautions (5.7)]*.

Hypersensitivity Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of severe hypersensitivity reactions. Advise latex-sensitive patients that the needle shield inside the removable cap of the CIMZIA prefilled syringe contains a derivative of natural rubber latex *[see Warnings and Precautions (5.4)]*.

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]*.

Preparation and Administration of CIMZIA Using the Prefilled Syringe

Instruct patients and caregivers on how to inject the Prefilled Syringe. Complete instructions are provided in the *Instructions for Use* packaged in each CIMZIA Prefilled Syringe kit.

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- If refrigerated, remove the prefilled syringe from the carton and let it warm to room temperature.
- Inspect the liquid in the prefilled syringe. It should be clear and colorless to yellow and free from particulates. Discard the syringe if cloudy, discolored or contains particulates.
- Suitable sites for injection include the thigh or abdomen. Inject at least 1 inch from the previous site.
- Do not inject into areas where the skin is tender, bruised, red or hard, or where there are scars or stretch marks.

Instruct patients and caregivers in proper syringe and needle disposal technique.

- To avoid needle-stick injury, do not to place the needle cap back on the syringe or otherwise recap the needle.
- Properly dispose of needles and syringes in a puncture-proof container.
- Do not reuse the injection materials.

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

US License No. 1736

Reference ID: 4410921

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 you 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 active non-radiographic axial spondyloarthritis (nr-axSpA) with measures of inflammation
- 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.
- are allergic to rubber or latex. The plastic needle shield inside the removable cap of the prefilled syringe contains natural rubber.
- 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.
- have or had serious blood conditions.
- 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. You and your doctor should decide if you should continue to take CIMZIA while you are pregnant. It is not known if CIMZIA will harm your unborn baby. **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, it 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 and at least 1 inch from your last injection.
- 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.**

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.** Get medical help right away if you have any signs of an allergic reaction which include a skin rash, swelling or itching of the face, tongue, lips, or throat, or trouble breathing.

  The plastic needle shield inside the removable cap of the prefilled syringe contains natural rubber and may cause an allergic reaction if you are sensitive to latex.
- **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. Tell your healthcare provider right away if you have any bruising, bleeding or a fever that does not go away.
- **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 information, 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: March 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Orig s237

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	October 17, 2013
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
BLA Number:	125160, Supplement 237 (axial spondyloarthritis) 125160, Supplement 215 (ankylosing spondylitis)
Applicant Name:	UCB, Inc.
Date of Submission:	December 17, 2012
PDUFA Goal Date:	October 17, 2013
Proprietary Name:	Cimzia
Established Name:	Certolizumab pegol
Dosage form:	200 mg lyophilized powder for reconstitution in a single-use vial with 1 mL of sterile water for injection 200 mg/mL solution in a single-use prefilled glass syringe
Strength:	200 mg/mL
Proposed Indications:	Active axial spondyloarthritis, including ankylosing spondylitis
Action:	Complete Response for axial spondyloarthritis Approval for ankylosing spondylitis

1. Introduction

UCB submitted this sBLA to support the indication of active axial spondyloarthritis (Axial SpA), including ankylosing spondylitis for Cimzia (certolizumab pegol) at a dose of 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks. Cimzia was first approved on April 22, 2008, for the treatment of Crohn's disease. Subsequently, it has been approved for rheumatoid arthritis (May 13, 2009), and psoriatic arthritis (September 27, 2013). The dose proposed for Axial SpA is the same as the dose for rheumatoid arthritis and psoriatic arthritis. The proposed general Axial SpA indication is unique, and no other drugs in the US have an Axial SpA indication. This summary review will provide an overview of the application, with a focus on the Axial SpA indication, and the efficacy data from the single clinical study submitted to support the indication.

Subsequent to submitting the application, the Applicant proposed to narrow the indicated population of Axial SpA to (b) (4) (b) (4) (b) (4) The ankylosing spondylitis (AS) indication was kept separate and later split into a separate sBLA.

2. Background

Spondyloarthritis (SpA) refers to a group of inflammatory diseases that share overlapping features, yet are heterogeneous in terms of clinical manifestations and disease severity. In general, patients are classified by whether they have predominantly axial involvement (Axial SpA) or predominantly peripheral involvement (Peripheral SpA). Various classification criteria have been proposed. [1, 2, 3, 4, 5] Axial SpA encompasses a spectrum of disease severity that spans from self-limited inflammation to bony destruction of the spine. Ankylosing spondylitis (AS) is a well-characterized, chronic and progressive form of Axial SpA. The majority of research performed over the last two decades has used the modified New York Criteria to identify patients with AS (Table 1). [6] These criteria were used in clinical trials performed to support product registration for AS in the United States.

Table 1. Modified New York criteria for ankylosing spondylitis (Source: van der Linden S. Arthritis Rheum 1984; 27:361-8)

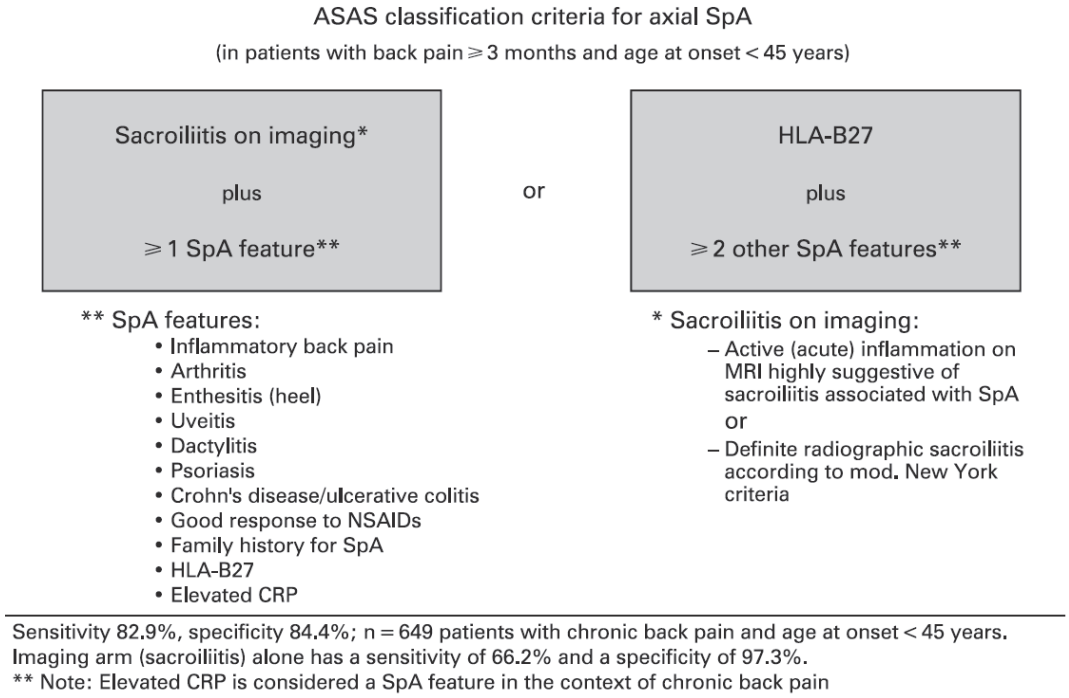
Clinical
• Low Back pain and stiffness for longer than 3 months, which improve with exercise, but are not relieved by rest
• Restriction of motion of the lumbar spine in both the sagittal and frontal planes
• Restriction of chest expansion relative to normal values correlated for age and sex
Radiographic
• Sacroiliitis grade ≥2 bilaterally, or grade 3-4 unilaterally
Definitive ankylosing spondylitis is present if the radiologic criterion is associated with at least one clinical criterion

The modified New York criteria have potential limitations in clinical practice as they are designed to identify patients with established AS with radiographic findings and do not identify all patients in the larger spectrum of inflammatory back pain. The Assessment of Spondyloarthritis International Society (ASAS) developed criteria for Axial SpA with the goal of identifying more patients in the spectrum of inflammatory back pain, including patients with early AS. [1, 2, 3] By design, these criteria were meant to be inclusive, as not to miss patients with the potential for developing progressive disease. The ASAS criteria for Axial SpA require patients to have back pain for at least three months and age of

[1] Rudwaleit M, van der Heijde D, Landewe R et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): validation and final selection. Ann Rheum Dis 2009; 68: 770-776.
[2] Rudwaleit M, van der Heijde D, Landewe R et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009; 68: 777-783.
[3] Sieper J, van der Heijde D, Landewe R et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). Ann Rheum Dis 2009; 68: 784-788.
[4] Amor B, Dougados M, Mijiyawa M. Criteria of the classification of spondyloarthropathies. Rev Rheum Mal Osterartic 1990; 57: 85-89.
[5] Dougados M, van der Linden S, Juhlin R et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 1991; 34: 1218-1227.
[6] Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984; 27: 361-368.

onset less than 45 years (Figure 1). One of the concerns is that patients with less specific clinical features would be classified as having Axial SpA, yet could have mechanical back pain, rather than inflammatory back pain.

Figure 1. ASAS classification criteria for Axial SpA



AS is a well-characterized progressive disease and four tumor necrosis factor (TNF) inhibitors have been approved for the treatment of AS. These are Enbrel (etanercept), Remicade (infliximab), Humira (adalimumab), and Simponi (golimumab). Patients studied in these AS development programs were diagnosed based on the modified New York Criteria (Table 1). These products have demonstrated efficacy in reducing signs and symptoms in AS, but it is not yet known whether these products have a beneficial effect on structural damage progression.

The Agency had various milestone regulatory meetings with the Applicant at various stages of the development program. An End-of-Phase 2 (EOP2) meeting was held in February 2010 regarding the broader axial spondyloarthropathy indication. At that time, UCB proposed a study where patients would meet ASAS criteria and would have sacroiliitis documented by x-ray or MRI. In light of this proposal, FDA indicated at that time that it seemed reasonable to use the ASAS criteria to select a broader population of patients with Axial SpA in order to capture patients with early AS. A pre-sBLA meeting was held in July 2012. At this meeting, FDA expressed concerns regarding a lack of clarity in the Axial SpA indication, what entities would be encompassed, and whether patients could evolve into diagnoses for which the risk-benefit profile of treatment would be unfavorable. FDA expressed concerns and indicated that discussion of the proposed

expanded Axial SpA indication in the setting of an advisory committee would likely be needed.

Some of the concerns and potential solutions related to drug development for Axial SpA are as follows:

- The ASAS criteria are non-specific and can potentially include patients with mechanical back pain. In future clinical studies, enrollment of patients with positive inflammatory markers such as positive MRI findings at the sacroiliac joints, elevated CRP at baseline, and both positive MRI findings at the sacroiliac joints and elevated CRP at baseline can possibly help address this issue. Of note, during review of this application, the Applicant proposed to revise the indication to patients wit (b) (4) (b) (4)
- AS and non-AS Axial SpA have overlapping clinical features, but seem to have many differences between them, such as the gender ratio and proportion of HLA-B27 positive patients. Future clinical studies should clearly separate these two entities to define the effect of a drug on the two entities separately.
- The natural disease course of Axial SpA may be variable and the long-term prognosis of patients with Axial SpA is not known. Future cohort studies will likely address this issue. In the interim, future clinical studies for drug development should be of long-term duration, such as 12 months, to provide information on the confounding effect of disease variability and symptom fluctuation over time.
- The risk-benefit of Cimzia or other biologic DMARDs for Axial SpA may be different than that for AS, particularly because the natural history of Axial SpA is not fully characterized and possibly there are a large number of patients who potentially satisfy the Axial SpA criteria. Long-term assessment, such as over 12 months, will help in determining risk-benefit assessment.

3. Chemistry, Manufacturing, and Controls

Cimzia is an approved marketed product and there are no CMC issues.

4. Nonclinical Pharmacology and Toxicology

No new non-clinical toxicology studies were required or performed for this application. The pharmacology and toxicology data were reviewed with the original application.

5. Clinical Pharmacology and Biopharmaceutics

No new clinical pharmacology studies were required or performed for this application. The clinical pharmacology data were reviewed with the original application.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

This submission is based on one study AS001, which included a 24-week placebo-controlled period, followed by 110-week open-label extension period. The application is based on submitted data through week 24.

b. Design and conduct of the studies

Study AS001 randomized patients 18 years of age and older meeting the ASAS criteria for Axial SpA (ASAS criteria were modified for this study to not use family history of Axial SpA and good response to NSAIDs as qualifying criteria). For the double-blind placebo-controlled period (through Week 24), patients were randomized 1:1:1 to Cimzia 200 mg subcutaneously (SC) every other week (following a loading regimen of 400 mg SC at Weeks 0, 2, and 4), Cimzia 400 mg SC every four weeks (following a loading regimen of 400 mg SC at Weeks 0, 2, and 4), or placebo. From Weeks 24 to 48, patients in the Cimzia treatment groups remained on their assigned dose regimen in a blinded fashion, and placebo patients were randomized to Cimzia at either 200 mg every other week or 400 mg every 4 weeks following the standard loading regimen. Placebo-treated patients were similarly randomized if they met criteria for "escape" at Week 16. After Week 48, patients remained on their assigned treatment in an open-label fashion for the duration of the extension period to 110 weeks.

The study was designed to enroll a sufficient number of patients with AS and non-radiographic axial spondyloarthritis (NR Axial SpA). The study called for 50% of patients fulfilling the modified New York criteria for AS. Of the remaining 50% of patients, at least 50% had to meet the ASAS MRI imaging criteria, and the remainder could be enrolled on the basis of clinical criteria only.

Patients enrolled in the study were classified into subgroups based on screening x-rays of the sacroiliac joints interpreted locally. At baseline, repeat x-rays of the sacroiliac joints were obtained and evaluated by central readers.

An MRI imaging sub-study was conducted at selected sites familiar with the MRI acquisition and scoring systems utilized for this study. Patients in the MRI substudy received MRI scans of the spine and sacroiliac (SI) joints at baseline, Week 12, Week 48, and Week 96 (or withdrawal visit).

The primary efficacy endpoint was the proportion of patients having an Assessment in Ankylosing Spondylitis (ASAS) 20 response at Week 12.

ASAS 20 response is defined as an improvement of at least 20% and an absolute improvement of at least 1 unit (on a scale of 0 to 10) in at least 3 of 4 domains, and no worsening in the remaining domain:

- Patient global assessment (Visual Analog Scale (VAS, 0 to 10))
- Total back pain (VAS 0 to 10)
- Function as assessed by the Bath AS Functional Index (BASFI)

- Inflammation, as assessed using the last two stiffness assessments in the Bath AS Disease Activity Index (BASDAI)

c. Efficacy findings and conclusions

The submitted data do not support efficacy of Cimzia in Axial SpA, but support efficacy of Cimzia in AS.

The results of the primary endpoint, proportions of ASAS 20 responders, for the overall Axial SpA patients, and subgroups of NR Axial SpA patients and AS patients based on local and central reading of plain x-ray films for sacroiliitis are shown in Table 2. Cimzia treatment groups had more ASAS 20 responders than the placebo group for the Axial SpA patients, and also in the two subgroups of NR Axial SpA and AS patients. The treatment differences between Cimzia and placebo were consistent for subgroups, irrespective of x-ray readers. Results of the secondary endpoints also showed a similar pattern (data not shown in this review).

Table 2. Primary endpoint – ASAS 20 response at week 12 in overall patients with axial spondyloarthritis (Axial SpA), and in subgroups of non-radiographic axial spondyloarthritis (NR Axial SpA) and ankylosing spondylitis (AS) by local and central x-ray interpretation status

	Placebo	Cimzia 200 mg Q2W	Cimzia 400 mg Q4W	Cimzia 200 mg and 400 mg Q4W
Axial SpA, N	107	111	107	218
Responders, %	38	58	64	61
Difference vs placebo, % [95% CI]	-	19 [6, 32]	25 [12, 38]	22 [11, 34]
NR Axial SpA, Local Reading, N	50	46	51	97
Responders, %	40	59	63	61
Difference to placebo, % [95% CI]	-	19 [-1, 38]	23 [4, 42]	21 [4, 38]
NR Axial SpA, Central Reading, N	35	33	30	63
Responders, %	20	42	47	44
Difference vs placebo, % [95% CI]	-	22 [1, 44]	26 [4, 49]	24 [6, 43]
AS, Local Reading, N	57	65	56	121
Responders, %	37	57	64	60
Difference to placebo, % [95% CI]	-	20 [3, 37]	27 [10, 45]	23 [8, 39]
AS, Central Reading, N	57	66	61	127
Responders, %	46	61	69	65
Difference vs placebo, % [95% CI]	-	15 [-3, 32]	23 [6, 41]	19 [4, 34]

A limitation of the study results (Table 2) was that some of the x-rays that were read centrally showed discordant results with the initial local x-ray reading. Local reading of the x-ray at screening was used originally to identify the subgroups of patients. X-rays were repeated at baseline and centrally read to evaluate consistency with locally read screening x-rays. As shown in Table 2, based on local x-ray reading, 147 patients had NR Axial SpA and 178 patients had AS (total of 325 patients), and based on central x-ray reading, 98 patients had NR Axial SpA and 184 patients had AS (total of 282 patients). Of the patients who had local x-ray reading, 43 patients did not have central x-ray

reading. Of these 43 patients, 37 had AS and 6 had NR Axial SpA based on local x-ray reading.

Discordance of results for NR Axial SpA is a potential problem because of the large difference in interpretation, 147 patients were classified as NR Axial SpA based on local x-ray reading and 98 patients were classified as NR Axial SpA based on central x-ray reading. This raises some uncertainty regarding robustness of the data from NR Axial SpA patients. Furthermore, although the difference between Cimzia and placebo in NR Axial SpA patients was consistent irrespective of whether local or central reading of x-rays were used to classify, this single study showing benefit in a sub-group of patients is not adequate as substantial evidence of efficacy in this novel indication with no regulatory precedence.

To overcome the uncertainty of the beneficial effect of Cimzia in NR Axial SpA, the Applicant will need to conduct at least one more study in patients who are clearly identified to have NR Axial SpA with objective signs of inflammation (positive MRI findings at the sacroiliac joints, or elevated baseline CRP, or both), and excludes patients with AS. The study results will need to demonstrate convincing efficacy benefit of Cimzia over placebo. The study will need to be 12-months in duration to assess the impact of possible fluctuation of disease severity over time, and also to provide long-term data for better risk-benefit assessment of Cimzia in NR Axial SpA. Such a study will help address some of the concerns discussed in section 2 above for drug development for NR Axial SpA.

Discordance of results with AS is a lesser problem because the number of patients classified as having AS remained consistent between local x-ray reading and central x-ray reading. The difference between Cimzia and placebo in AS patients was consistent irrespective of whether local or central x-ray reading of x-rays were used to classify, and was also consistent with the sensitivity analysis with 43 patients who did not have central x-ray reading (data not shown in this review). The submitted data from this single study are adequate as substantial evidence of efficacy for AS because TNF inhibitors as a class are known to be efficacious in AS, and there is regulatory precedents of approving TNF inhibitors for AS based on a single study.

8. Safety

a. Safety database

New safety data submitted with this application are from the 24-week placebo-controlled treatment period of the single study AS001 discussed above in section 7.

b. Safety findings and conclusion

The new safety data do not raise any new safety concerns for Cimzia. The safety findings remain consistent with previous findings.

c. REMS/RiskMAP

Cimzia does not currently have REMS, but does have a medication guide to communicate the risks of serious infections, including tuberculosis, invasive fungal infections, hepatitis B reactivation, and malignancy, consistent with other approved TNF inhibitors. No new safety signals were identified in this submission that would warrant a change in this status.

9. Advisory Committee Meeting

A two-day meeting of the Arthritis Advisory Committee (AAC) was held on July 22 and 23, 2013. The topic on the first day was a general discussion of the ASAS classification criteria of Axial SpA for drug development. The second day was a product-specific discussion of the sBLAs for Humira for NR Axial SpA, and Cimzia for Axial SpA, including ankylosing spondylitis (this application).

Regarding the general discussion of the ASAS classification criteria for Axial SpA, Committee members noted that longer-term data are needed to understand the natural history of the disease, but did not believe this would preclude use of Axial SpA as an indication before those data were available. A major concern was the potential for misclassification of patients with mechanical back pain with Axial SpA. To address this concern, the majority of the panel indicated that the use of objective measures of inflammation would be helpful, in particular, MRI of the sacroiliac joints.

Regarding this sBLA for Cimzia, Committee members expressed uncertainty regarding the submitted efficacy data, particularly the definition of "active" Axial SpA, and the small number of patients exposed to support the novel indication. The Committee was favorable regarding demonstration of efficacy (voted 8 to 5, with 1 abstention). The voting efficacy question was inclusive of the Axial SpA and the AS indications. The Committee was more comfortable with the AS indication, but not the Axial SpA indication. The Committee was favorable regarding the safety profile of Cimzia (voted 13 to 1 with 1 abstention), but expressed concern regarding the safety implication of misclassification of mechanical back pain with Axial SpA. Overall, the Committee was split on the question of approval of Cimzia for Axial SpA, including AS (voted 7 yes, 6 no, and 1 abstention).

10. Pediatric

The applicant requested a full waiver from Pediatric Research Equity Act (PREA) requirements with the reasoning that studies in children with Axial SpA or AS would be impossible or impractical to conduct because of the rarity of the diagnosis in children. This application was discussed at a Pediatric Review Committee (PeRC) meeting on August 14, 2013, and the PeRC agreed with granting a full waiver.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audit was not conducted because the efficacy data did not appear to be questionable. Each study site enrolled a small number of patients and, therefore, an audit of even several sites was unlikely to be informative. During review of the submission, no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with the acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. No potentially conflicting financial interests were identified.

c. Others

There are no outstanding issues with consults received from OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There is no issue with the proposed proprietary name as the name Cimzia was previously reviewed and found to be acceptable. The product is currently marketed under the trade name Cimzia.

b. Physician Labeling

The labeling of Cimzia was reviewed previously with the original approval of the product. With this application, the existing label will be updated to include new information regarding the claim of treating patients with AS. The main changes will reflect new data from the AS subgroup from the single study submitted with this sBLA.

c. Carton and Immediate Container Labels

Cimzia is a marketed product and there were no changes to the carton and immediate container labels with this application. These were reviewed previously by various disciplines of this Division, and the current version was found to be acceptable.

d. Patient Labeling and Medication Guide

These will be updated to reflect the new AS indication.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The Applicant has not submitted adequate data to support approval of Cimzia in adult patients with active Axial SpA (original proposal), or adult patients with NR Axial SpA (b) (4) (b) (4) (b) (4) (revised proposal). However, the submitted data are adequate to support approval

of Cimzia in adult patients with AS. The action on this application will be Complete Response for the Axial SpA indication (supplement 237) and Approval for the AS indication (supplement 215).

Recommended comments for the action letter:

The submitted data from study AS001 do not provide substantial evidence to support the use of Cimzia in patient (b) (4) (b) (4) (b) (4) The targeted population (those with objective signs of inflammation) for the indication is a subgroup of the overall study population, which has not been studied adequately to demonstrate efficacy and safety.

To support approval of Cimzia for the proposed indication in the target population, provide efficacy and safety data from at least one controlled 12-month study in patients who are clearly identified to have non-radiographic axial spondyloarthritis. Exclude patients with other types of arthritis known to be responsive to Cimzia from the study. Ensure adequate representation of patients in each of these groups: positive MRI findings at the sacroiliac joints, elevated CRP at baseline, and both positive MRI findings at the sacroiliac joints and elevated CRP at baseline. Consider other factors that may impact the effect of treatment, such as duration of disease, and prior use of therapy. Develop and submit plans for risk mitigation and safe use of Cimzia in the targeted population.

b. Risk Benefit Assessment

The overall risk benefit assessment does not support approval of Cimzia for use in patients with active Axial SpA (original proposal broad indication) (b) (4) (b) (4) (b) (4) (b) (4) (revised proposed narrowed indication). The submitted efficacy data are not adequate to demonstrate efficacy in Axial SpA as discussed in section 7 above. There are also some uncertainties regarding the ASAS criteria for diagnosing Axial AS, as discussed in sections 2 and 7 above. The submitted safety data do not show any new safety concerns in Axial SpA, but it is difficult to make a risk-benefit assessment without demonstration of efficacy and also because the database for the targeted patients is small. However, the submitted data are adequate to support approval of Cimzia in adult patients with AS. The submitted efficacy data are adequate to demonstrate efficacy in AS as discussed in section 7 above. The safety data do not raised any new concerns for Cimzia.

c. Post-marketing Risk Management Activities

There are no new postmarketing risk management activities that will be required on the basis of this submission.

d. Post-marketing Study Commitments

There are no new post-marketing requirements or commitments based on review of this submission.

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/s/

BADRUL A CHOWDHURY
10/17/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Origs237

MULTI-DISCIPLINE REVIEW

Summary Review
Cross Discipline Team Leader Review
Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplement
Application Number(s)	125160/s237
Priority or Standard	Priority
Submit Date(s)	September 28, 2018
Received Date(s)	September 28, 2018
PDUFA Goal Date	March 28, 2019
Division/Office	DPARP/ODEII
Review Completion Date	March 27, 2019
Established/Proper Name	Certolizumab pegol
(Proposed) Trade Name	CIMZIA®
Pharmacologic Class	TNFα inhibitor
Applicant	UCB, Inc.
Doseage form	200 mg/mL in a single-dose prefilled syringe
Applicant proposed Dosing Regimen	400 mg initially and at Weeks 2 and 4, followed by 200 mg every 2 weeks or 400 mg every 4 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with non-radial axial spondyloarthritis (nr-axSpA) with objective signs of inflammation
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation
Recommended Dosing Regimen	400 mg initially and at Weeks 2 and 4, followed by 200 mg every 2 weeks or 400 mg every 4 weeks

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Nina Ton, PharmD
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Office of Clinical Pharmacology Team Leader(s)	Anshu Marathe, PhD
Clinical Reviewer	Suzette Peng, MD
Clinical Team Leader	Rachel Glaser, MD
Statistical Reviewer	William Koh, PhD
Statistical Team Leader	Lei Nie, PhD
Cross-Disciplinary Team Leader	Rachel Glaser, MD
Designated Signatory Authority (DPARP)	Nikolay Nikolov, MD

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Patient Labeling	Aman Sarai, BSN, RN; Marcia Britt Williams, PhD

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Dipak Pisal	OCP/DCPII	Section:6	**Select one:** _X_ Authored _X__ Approved
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Clinical Pharmacology Team Leader	Anshu Marathe	OCP/DCPII	Section: 6	**Select one:** ___ Authored _X_ Approved
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Clinical Reviewer	Suzette Peng	ODEII/DPARP	Sections: 1-5, 7-16	**Select one:** _X_ Authored _X__ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Division Director or Designated Signatory	Nikolay Nikolov	ODEII/DPARP	Sections: All	**Select one:** ___ Authored _X__ Approved
	Signature: Nikolay P. Nikolov -S Digitally signed by Nikolay P. Nikolov -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011314790, cn=Nikolay P. Nikolov -S Date: 2019.03.28 11:09:21 -04'00'			
Statistical Reviewer	William Koh	DB2/OB	Sections: 7.2, 8, 16	**Select one:** _X__ Authored _X__ Approved
	Signature: William Jen Hoe Koh -S Digitally signed by William Jen Hoe Koh -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002137835, cn=William Jen Hoe Koh -S Date: 2019.03.28 07:30:36 -04'00'			
Statistical Team Leader	Lei Nie	DB2/OB	Sections: 7.2, 8, 16	**Select one:** ___ Authored _X__ Approved
	Signature: Lei Nie -S Digitally signed by Lei Nie -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lei Nie -S, 0.9.2342.19200300.100.1.1=1300430387 Date: 2019.03.28 08:03:07 -04'00'			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
AS	ankylosing spondylitis
axSpA	axial spondyloarthritis
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
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
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CZP	certolizumab pegol
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
nr-axSpA	nonradiographic axial spondyloarthritis
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBO	placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRN	as needed
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Certolizumab pegol (CZP, CIMZIA®) is a humanized fragment antigen binding prime (Fab') conjugated to polyethylene glycol (PEG) which targets tumor necrosis alpha (TNFα or TNF). CZP neutralizes human TNFα bioactivity and also inhibits the production of inflammatory cytokines by monocytes. Because it does not include an Fc region, it does not induce complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, or other cytotoxicity such as apoptosis and degranulation. CZP is approved in the US for the treatment of adults with Crohn's disease (CD), rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and psoriasis (PsO). It is available as a single-use vial (lyophilized powder for reconstitution, 200 mg) or a pre-filled syringe (200 mg) for subcutaneous (SC) injection.

UCB is resubmitting supplement 237 to Biological Licensing Application (BLA) 125160 for CZP for the treatment of non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation. This supplement originally received a Complete Response for this population on October 17, 2013. A history of the previous submission and other pertinent regulatory history is provided in Section 3. The proposed dose is CZP 400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week (Q2W) or 400 mg every 4 weeks (Q4W). No changes to the currently marketed presentations are being proposed in this supplemental BLA (sBLA).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Study AS0006, a 52-week, double-blind, placebo-controlled study with 317 patients with nr-axSpA, provides the primary evidence for the effectiveness of CZP for the treatment of nr-axSpA in this resubmission. This study was conducted after the Complete Response and addressed many of the concerns expressed in the Complete Response letter, such as study duration as well as adequate measures of inflammation at baseline to ensure the selection of patients for whom the benefit-risk can be adequately characterized. As further supportive evidence of effectiveness, UCB included data from study AS001, a 24-week, double-blind, placebo-controlled study with 98 patients with nr-axSpA (based on central radiographic read). AS001 was the original study submitted for this proposed indication that was given a Complete Response. Reviewed and considered together, both studies meet the statutory evidentiary standard for effectiveness.

The primary endpoint for study AS0006 was ASDAS-MI response at Week 52. More patients on CZP 200 mg Q2W (47%) compared to patients on PBO (7%) experienced a clinical response, and the difference was statistically significant ($p<0.001$). ASAS40 was a major secondary endpoint and was considered important for interpretation of the efficacy of CZP for nr-axSpA, as there is

regulatory precedent of its use in the approval for a related condition, ankylosing spondylitis (AS or radiographic axSpA). At Week 52, there was a greater proportion of patients on CZP (56.6%) than patients on PBO (15.8%) who achieved ASAS40 response, and the difference was again statistically significant ($p<0.001$).

The chronic dosing of CZP 400 mg Q4W was not studied in AS0006. Instead, UCB relied on the data from AS001 which studied the two chronic CZP dosing regimens, 400 mg Q4W and 200 mg Q2W, proposed for labeling. At the time of original submission, it was determined that the number of patients with nr-axSpA, based on a central read of the baseline radiographs, was too small (N=98 with just 63 patients on CZP and 35 patients on PBO) and not sufficient as a single study to allow for a regulatory decision. However, it is adequate as a supportive study to AS0006. In AS001, more patients on CZP (33.3%) had an ASAS40 response at Week 12 compared to patients on PBO (11.4%). The ASAS40 response was similar for both doses of CZP (30.3% on 200 mg Q2W and 36.7% on 400 mg Q4W). Thus, the efficacy results for both doses of CZP from study AS001 support the results from study AS0006 and the proposed dosing regimens.

In conclusion, study AS0006 provides substantial evidence on the efficacy of CZP 200 mg Q2W and results from study AS001 were supportive of the efficacy of the CZP 400 mg Q4W (with the same loading dose of CZP 400mg initially and at Weeks 2 and 4) for the treatment of nr-axSpA with objective signs of inflammation.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Axial spondyloarthritis (axSpA) is an inflammatory arthritis of the axial skeleton (sacroiliac joints and spine). The 2009 ASAS criteria provided new classification criteria for axSpA. Patients were classified as having nonradiographic axial spondyloarthritis (nr-axSpA) if they met ASAS criteria for axSpA but did not meet modified New York (mNY) criteria for ankylosing spondylitis (AS). Thus, patients with nr-axSpA do not have radiographic evidence of sacroiliitis. Although therapies are approved for AS in the US, there are no therapies currently approved for nr-axSpA in the US.

Certolizumab pegol (CZP, CIMZIA®) is a humanized fragment antigen binding prime (Fab') conjugated to polyethylene glycol (PEG) which targets tumor necrosis alpha (TNFα or TNF). CZP is approved in the US for the treatment of adults with Crohn's disease (CD), rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and psoriasis (PsO). UCB submitted two phase 3 trials to support the treatment of active nr-axSpA with objective signs of inflammation (MRI+/CRP-, MRI-/CRP+, MRI+/CRP+). The principal pivotal trial (AS0006) was a 52-week, double-blind, placebo-controlled study to evaluate CZP 200 mg Q2W. The second efficacy study (AS001) was a 24-week, double-blind, placebo-controlled trial to evaluate two dosing regimens, CZP 200 mg Q2W and CZP 400 mg Q4W. Together, these studies provided the substantial evidence for effectiveness of both doses of CZP to improve signs and symptoms, as measured by Ankylosing Spondylitis Disease Activity Score (ASDAS) and Assessment in SpondyloArthritis international Society (ASAS) response. AS0006 also showed improvement of CZP over PBO in several patient-repoted outcomes (PROs) (e.g., the Bath Ankylosing Spondylitis Functional Index [BASFI] and Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]) and health-related outcomes (e.g., Ankylosing Spondylitis Quality of Life [ASQoL]).

Overall, more adverse events (AEs) occurred in the CZP-treated patients compared to the PBO-treated patients during the double-blind periods of studies AS0006 and AS001. However, the number of serious adverse events (SAEs) and AEs leading to discontinuation was low and similar in both treatment groups. No deaths occurred in the nr-axSpA program. Overall, the safety profile of CZP in the treatment of nr-axSpA is consistent with the previous experience with CZP.

In conclusion, the resubmission of supplement 237 has provided adequate data to inform the benefit-risk assessment of CZP for the treatment of nr-axSpA. The benefit-risk profile is favorable to support both the 200 mg Q2W and the 400 mg Q4W chronic dosing regimens for the proposed indication. Both doses showed efficacy for clinical assessments in nr-axSpA. The safety was consistent with the known safety of CZP and offered an acceptable risk for the therapeutic benefits of CZP. Certolizumab pegol would provide the first treatment option in the US for patients with nr-axSpA who have objective measures of inflammation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Nonradiographic axial spondyloarthritis (nr-axSpA) is a diagnosis based on ASAS classification criteria. These criteria potentially allow for the earlier diagnosis of axial spondyloarthritis (axSpA). AxSpA describes an inflammatory arthritis that affects the spine and/or sacroiliac joints. Patients classically have inflammatory back pain. Patients, who meet ASAS criteria for axSpA but do not meet radiographic criteria for ankylosing spondylitis (AS), are diagnosed with nr-axSpA. • ASAS criteria require that patients have back pain ≥ 3 months with the age of onset < 45 years. Patients could then be classified as having axSpA based on meeting clinical criteria or radiographic criteria. The clinical path requires HLA-B27 positivity and ≥ 2 additional features (e.g., inflammatory back pain, arthritis, enthesitis, response to NSAIDs, family history, elevated CRP). The radiographic path requires sacroiliitis on imaging and ≥ 1 clinical feature. Thus, patients with nr-axSpA could not have conventional radiographic evidence of sacroiliitis (i.e., meeting modified New York [mNY] criteria) but could have MRI evidence of sacroiliitis. • It has been suggested that nr-axSpA may be an early presentation of AS, but there are many patients who do not progress. Some risks for disease progression that have been considered include male gender, longer disease duration, elevation in CRP, and MRI evidence of sacroiliitis. • Because these are new criteria, the prevalence of this disease has been difficult to determine. However, it was proposed in 2013 that approximately 500,00 people aged 18-44 years had nr-axSpA in the US.	Nonradiographic axial spondyloarthritis (nr-axSpA) is an inflammatory arthritis of the axial skeleton without evidence of sacroiliitis on conventional radiographs. Patients with nr-axSpA can have inflammatory back pain that can impact quality of life. These patients may or may not progress to evidence of radiographic sacroiliitis (ankylosing spondylitis).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Recommendations for treatment are based on literature for ankylosing spondylitis (AS). • No therapy is approved for nr-axSpA in the US. • Standard of care for nr-axSpA begins with treatment with NSAIDs. • According to several treatment guidelines (ACR/SPARTAN, EULAR/ASAS), patients with nr-axSpA who have persistent disease activity can be treated with TNF inhibitors or potentially other biologic DMARDs.	At this time, there are no approved therapies for nr-axSpA. Although many patients with nr-axSpA may respond to routine NSAIDs, there are many patients who cannot maximize NSAID use because of adverse effects or lack of adherence. There are also patients who remain symptomatic despite NSAID therapy.
Benefit	• Certolizumab pegol (CZP) is proposed for the treatment of adult patients with non-radiographic axial spondyloarthritis with objective evidence of inflammation. • The efficacy of CZP was supported by a 52-week, double-blind, placebo-controlled study to evaluate efficacy and safety of CZP 200mg Q2W in patients with nr-axSpA (n=317). • As a 12-month study, AS0006 could potentially offer some insight into the natural history of nr-axSpA and also help in assessment of risk-benefit of the intervention. Additionally, the study included representation of all potential manifestations of inflammation at baseline, i.e., MRI+/CRP-, MRI-/CRP+, and MRI+/CRP+. • AS001 was a 24-week, double-blind, placebo-controlled study to evaluate efficacy and safety of CZP (200mg Q2W and 400mg Q4W) in patients with nr-axSpA. Concerns arose during the original review of this study because there were discrepancies between the local reads of screening radiographs and the central reads of baseline radiographs in terms of meeting mNY criteria for AS. Utilizing patients who were categorized as nr-axSpA by central radiographic reads, the total number of patients was 98. This was not sufficient as the only study for this patient population,	Study AS0006 was adequate and well-controlled. Though the number of patients in study AS001 was low, it was adequate to provide support to the results from AS0006. Certolizumab 200mg Q2W and 400mg Q4W show benefit for the treatment of signs and symptoms of nr-axSpA. At this time, in the US, patients with nr-axSpA do not have any other options other than NSAIDs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	but it is acceptable as a supportive study. • The primary endpoint in study AS0006 was proportion of patients who achieved ASDAS-MI at Week 52. • ASDAS is a weighted calculation of components of patient global assessment, neck/back/hip pain, duration of morning stiffness, peripheral pain/swelling, and CRP. Active disease is defined as an ASDAS ≥2.1, and ASDAS-MI (ASDAS Major Improvement) is a reduction of ASDAS ≥2. • 47% of patients on CZP 200mg Q2W achieved ASDAS-MI at Week 52 compared to 7% of patients on PBO. The difference was statistically significant. • An important secondary endpoint was the proportion of patients who achieved ASAS40 at Week 52. There is more regulatory history for the use of ASAS reponse for the indication of AS. • ASAS response is made up of domains including patient global assessment, total spinal pain, BASFI, morning stiffness, and duration of morning stiffness. ASAS40 is defined as a relative improvement of at least 40% and absolute improvement of at least 2 units (0 to 10 NRS) in at least 3 of the 4 domains. • A greater proportion of patients on CZP (56.6%) achieved ASAS40 response compared to patients on PBO (15.8%), and the difference was statistically significant. • In study AS001, the efficacy assessments included ASAS response at Week 12. • More patients on CZP (33.3% overall) achieved ASAS40 response compared to patients on PBO (11.4%). The proportion of patients on each dose of CZP was similar, 30.3% on CZP 200 mg Q2W and 36.7% on 400 mg Q4W.	APPEARS THIS WAY ON ORIGINAL

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Risk and Risk Management	• Data from studies AS0006 and AS001 (CZP 200mg Q2W dose) through the double-blind period provided the primary safety pool (Pool S1) for consideration. Additionally, a larger safety pool (Pool S2) included data from all studies with CZP and patients with nr-axSpA. This not only included the double-blind periods of both studies but also included the escape and OL periods as well as both doses of CZP (200mg Q2W and 400mg Q4W). There are also 2 ongoing studies with patients with nr-axSpA (AS0005 and AS0007), and the data from these studies were included in study Pool S2.
	• Pool S1 included the safety data of approximately 180 patients who received CZP and a similar number who received PBO.
	• The overall number of safety events was low in the nr-axSpA program, particularly for SAEs and AEs leading to discontinuation. No deaths occurred.
	  ○ One serious infection (neuroborreliosis) occurred in a patient on CZP in Pool S1.
	  ○ Four patients on CZP in Pool S2 experienced opportunistic infections (2 cases of TB, 1 case of legionella pneumonia, 1 non-serious case of esophageal candidiasis).
	  ○ Three malignancies (malignant melanoma, basal cell carcinoma, and astrocytoma) occurred in patients on CZP in Pool S2.
	  ○ More patients on CZP developed an elevation in liver-associated enzymes and creatine kinase. These elevations were not clinically significant.
	• Given the low numbers, it is difficult to make conclusions about safety. However, the types of events were consistent with the known safety profile of CZP.
		The safety profile was consistent with and no worse than the known safety profile of CZP for other indications.
		
		No new safety signals were identified to require further risk management.
		
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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There were no new safety signals.	

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		8.1
		x	Patient reported outcome (PRO)	8.1
		☐	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	8.1
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Spondyloarthritis (SpA), also referred to as "seronegative spondyloarthritis," are a group of inflammatory arthritides that share similar genetic, epidemiologic, and radiologic manifestations. These spondyloarthritides include ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, inflammatory bowel disease (IBD)-associated arthritis, and undifferentiated spondyloarthritis. Axial spondyloarthritis (axSpA) is the term used to describe the SpA that primarily affect the axial skeleton, namely, the spine and sacroiliac joints. Common clinical manifestations of these patients include inflammatory back pain and enthesitis. AS has classically defined this category. The modified New York (mNY) criteria (developed in the 1980s, Table 1) have been the most commonly used classification criteria for AS and have required the presence of sacroiliitis on x-ray.

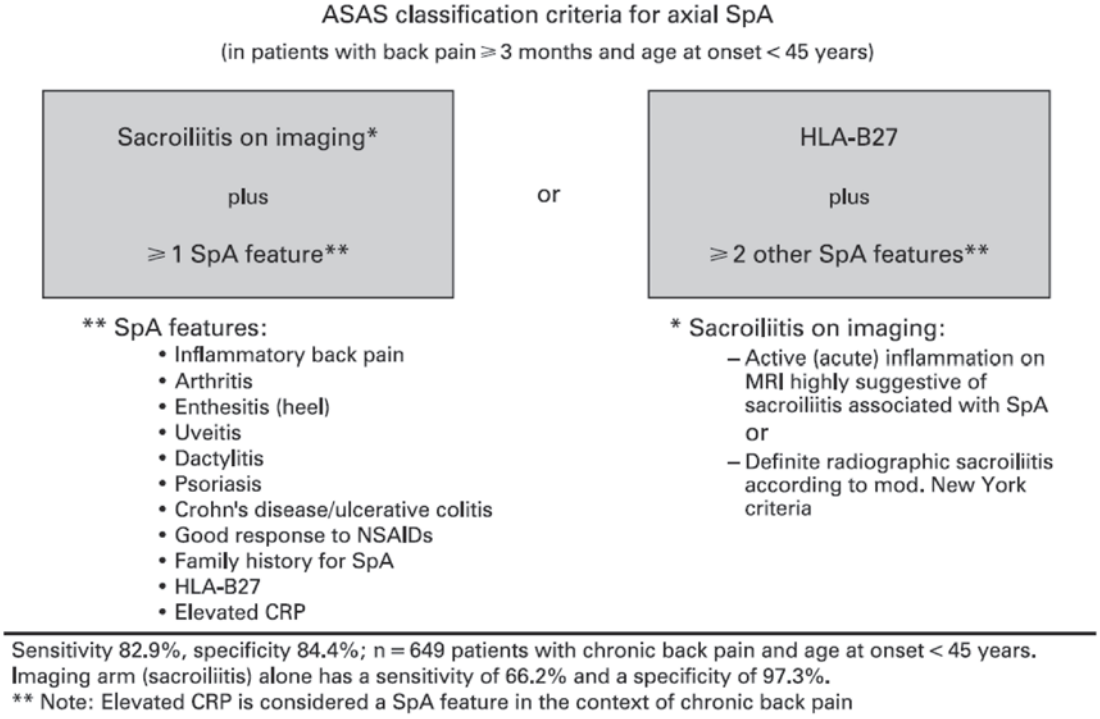
Table 1. Modified New York (mNY) Classification Criteria for Ankylosing Spondylitis

Clinical Criteria
• Low back pain and stiffness for longer than 3 months, which improve with expercise but are not relieved by rest • Restriction of motion of the lumbar spine in both the saggital and frontal planes • Restriction of chest expansion relative to normal values correlated for age and sex
Radiologic Criterion
• Sacroiliitis grade ≥ 2 bilaterally or Grade 3-4 unilaterally
Definite ankylosing spondylitis (AS) is present if the radiologic criterion is associated with at least one of the clinical criteria.

[Source: van der Linden S, et al. *Arthritis Rheum*, Table 8. 27; 1984: 366.]

Over the years, there has been greater recognition that early sacroiliitis may not be captured on plain radiograph and that clinical symptoms may precede changes on radiograph. In 2009, the Assessment of SpondyloArthritis international Society (ASAS) developed a new set of classification for axSpA in order to describe a broader spectrum of inflammatory back pain, including those patients who do not have radiographic sacroiliitis. These criteria (Figure 1) required that patients must have back pain ≥ 3 months with the age of onset < 45 years. There are then 2 paths to meet criteria for axSpA. The clinical path requires positive HLA-B27 and 2 or more additional features (e.g., inflammatory back pain, arthritis, enthesitis, uveitis, etc.), whereas the radiographic path requires sacroiliitis on imaging and 1 or more clinical feature. Sacroiliitis could either be x-ray findings consistent with the mNY criteria (thus, AS or radiographic axSpA) or MRI findings suggestive of sacroiliitis. The term **nonradiographic axial spondyloarthritis (nr-axSpA)** is used to describe patients who meet ASAS criteria for axSpA but do not meet mNY criteria for AS.

Figure 1. ASAS Classification Criteria for Axial Spondyloarthritis (axSpA)



[Source: Rudwaleit M, et al. *Ann Rheum Dis*, Figure 2. 2009; 68: 781.]

At the time of the first submission of Supplement 237 (2012), there remained questions about the use of the term axSpA because of the clinical heterogeneity encompassed by the ASAS criteria. The range of clinical presentations could be a patient with HLA-B27 and a family history of SpA (*without* inflammatory back pain) to a patient with MRI findings suggestive of sacroiliitis and uveitis. Additionally, the prevalence and natural history of nr-axSpA were unknown. Since that time, there has been greater understanding and acceptance of the ASAS criteria by the community, as evidenced by many professional and academic societies utilizing these criteria to make recommendations and guidelines for treatment (see Section 2.2).

Utilizing the ASAS criteria, it has been estimated that 0.7% of the population aged 18-44 years (slightly less than 1 million people) have axSpA.[1] Approximately half of the overall axSpA population have nr-axSpA. More females have nr-axSpA (2:1, female:male), whereas AS is more common in males (2 to 3:1). The concept of progression of disease and the spectrum of axSpA have been further considered. For some patients, nr-axSpA may be an "early AS" or "pre-AS," but there are other patients with nr-axSpA who have had disease for many years and

[1] Strand V, Rao S, Shillington A, et al. *Arthritis Care Res*. 2013; 65: 1299-306.

have not shown any progression.[2] Some observational studies have suggested that progression is 10-12% in the first 2 years, 20-25% about 2-8 years after diagnosis, and 26-28% after ≥10 years.[3] Prospective studies may suggest a lower rate of progression. Male gender, elevated CRP, and MRI changes consistent with sacroiliitis may be predictors of progression.[4] In general, however, there remains a need for more studies to understand the natural history of nr-axSpA and predictive risk factors for disease progression.

2.2. Analysis of Current Treatment Options

The American College of Rheumatology (ACR), together with the Spondyloarthritis Research and Treatment Network (SPARTAN) and the Spondylitis Association of America (SAA), published 2015 recommendations for the treatment of AS and nr-axSpA.[5] Subsequently, the European League Against Rheumatism (EULAR) with ASAS published a 2016 update of their recommendations for management of axSpA.[6] Overall, these organizations' recommendations for treatment were similar. Both guidelines also relied on the literature from AS, as the data on treatment for nr-axSpA were limited.

Patients with nr-axSpA may benefit from nonpharmacologic and lifestyle interventions such as home exercise and physical therapy to maintain flexibility and normal posture, as well as tobacco cessation.[7] Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line pharmacologic therapy for nr-axSpA. There is no role for disease-modifying antirheumatic drugs (DMARDs) for purely axial disease. ACR conditionally recommended anti-TNFα therapy in adults with active nr-axSpA despite treatment with NSAIDs. The EULAR/ASAS guidelines made the same recommendations but also added that patients should be re-evaluated after 12 weeks of therapy. Treatment response should be evaluated by a disease activity measure (e.g., BASDAI [Bath Ankylosing Spondylitis Disease Activity Index] or ASDAS [Ankylosing Spondylitis Disease Activity Score]), and, if the patient has not had an adequate response, treatment should be switched to a different anti-TNF inhibitor or even an anti-IL-17 inhibitor. If patients show sustained remission, biologic DMARDs may be weaned.

At this time, there are no FDA-approved therapy for nr-axSpA. In Europe, the EMA has recommended approval of several anti-TNFα therapies for nr-axSpA, specifically, etanercept (ETN), adalimumab (ADA), CZP, and golimumab (GOL).

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[2] Ghosh and Ruderman. *Arthritis Res Ther*. 2017; 19: 286-295.
[3] Ibid.
[4] Ibid.
[5] Ward M, Deodhar A, Akl E, et al. *Arthritis Rheumatol*. 2016; 68: 282-298.
[6] van der Heijde D, Ramiro S, Landewé R, et al. *Ann Rheum Dis*. 2017; 76: 978-991.
[7] Lockwood M and Gensler L. *Best Pract Res Clin Rheumatol*. 2017; 31: 816-819.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Certolizumab pegol (CZP) first became available in Switzerland on January 3, 2008, for patients with Crohn's Disease (CD). The US Food and Drug Administration (FDA or the Agency) has since approved CZP for multiple indications as described in Table 2.

Table 2. FDA Approval History of Certolizumab Pegol (CZP)

Indication	Date of Approval	Approved Dose
Reducing the signs and symptoms of **Crohn's Disease (CD)** and maintaining clinical response in adult patients with moderately to severely active disease with inadequate response to conventional therapy *BLA 125160*	April 22, 2008	400mg initially and at Weeks 2 and 4, followed by 400mg Q4W
Treatment of adult patients with moderately to severely active **rheumatoid arthritis (RA)** *BLA 125160/supplement 80*	May 13, 2009	400mg initially and at Weeks 2 and 4, followed by 200mg Q2W. For maintenance dosing, 400mg Q4W can be considered.
Treatment of adult patients with active **psoriatic arthritis (PsA)** *BLA 125160/supplement 213*	September 27, 2013	400mg initially and at Weeks 2 and 4, followed by 200mg Q2W. For maintenance dosing, 400mg Q4W can be considered.
Treatment of adults with active **ankylosing spondylitis (AS)** *BLA 125160/supplement 215*	October 17, 2013	400mg initially and at Weeks 2 and 4, followed by 200mg Q2W or 400mg Q4W
Treatment of adults with moderate-to-severe **plaque psoriasis (PsO)** who are candidates for systemic therapy or phototherapy *BLA 125160/supplement 283*	May 29, 2013	400mg Q2W. For some patients (body weight ≤ 90kg), 400mg initially and at Weeks 2 and 4, followed by 200mg Q2W may be considered.

Abbreviations: Q2W=every other week; Q4W=every 4 weeks
[Source: Clinical Reviewer]

Regulatory History of Supplement 237

Efficacy supplement 215 was submitted on December 12, 2012, at which time the Applicant originally was seeking the indication of active axial spondyloarthritis (axSpA) including ankylosing spondylitis (AS). The supplement was supported by data from study AS001, a 24-week, double-blind, placebo-controlled study with a 110-week open-label extension period in 325 patients who met the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axSpA. The study was designed to enroll a sufficient number of patients with both AS (defined by modified New York [mNY] criteria) and nr-axSpA. Specifically,

half of the patients should have fulfilled criteria for AS, and the other 50% have nr-axSpA. There were 3 treatment arms: PBO vs. CZP 200 mg Q2W vs. CZP 400 mg Q4W. All treatment arms received a loading dose; in the CZP arms, the loading dose was CZP 400mg at Weeks 0, 2, and 4. The primary endpoint was ASAS20 at Week 12.

During the review, it was noted that there were discrepancies between the local and central reads of screening and baseline sacroiliac (SI) radiographs, respectively. Consequently, there was significant misclassification, particularly for patients with nr-axSpA, and the subgroup of patients with nr-axSpA could be as few as 98 patients. Utilizing the data based on central reader interpretation, the nr-axSpA subgroup was associated with a lower proportion of ASAS20 responders compared to the AS group, but the difference from placebo (PBO) was similar between both subgroups.

An Arthritis Advisory Committee (AAC) meeting was held on July 22-23, 2013, to discuss the ASAS classification criteria for axSpA, the potential implications of using these criteria to define an indication for drug approval, and then a product-specific (adalimumab and certolizumab pegol) discussion of the sBLAs for this indication.[8] The Committee members noted that longer term data are needed to understand the natural history of populations who are defined as having axSpA by the ASAS criteria but that this need for data did not preclude its use as an indication for drug approval. In terms of the sBLA of CZP for active axSpA, the Committee was divided as to whether the data from AS001 provided substantial evidence for overall approval of CZP for the treatment of active axSpA, including patients with AS (7 yes, 6 no, 1 abstain). The Committee members commented that the definition of "active" axSpA was unclear, that the ability to characterize patients into subgroups of AS and nr-axSpA may be limited due to x-ray classification, and that it was uncertain whether the small number of patients exposed was sufficient to support efficacy in the new indication. After completion of the review, the Agency concluded that study AS001 did not provide adequate evidence of efficacy and safety of CZP in the nr-axSpA subgroup and, thus, the broader indication of active axSpA. Supplemental BLA 215 was split into 2 supplements: AS (supplement 215) and nr-axSpA (supplement 237). The Agency approved CZP for the indication for AS (supplement 215). However, the Applicant received a Complete Response (CR) for the broader indication of axSpA patients who do not have AS (supplement 237). The CR letter for Supplement 237 included the following issues and recommendations:

- The submitted data from AS001 are inadequate to support approval of CZP for the treatment of patients with axSpA. The proposed populations for a broader axSpA indication have not been studied adequately to demonstrate efficacy and safety.

[8] https://wayback.archive-it.org/7993/20170403223725/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm354581.htm

- To support approval of CZP for the broader axSpA indication, the Applicant should provide efficacy and safety data from at least one controlled 12-month trial in patients who are clearly identified to have nr-axSpA. The study should exclude patients with AS. The study protocol should ensure adequate representation of patients in each of the following groups: (+) MRI findings at the SI joints, elevated CRP at baseline, and both (+) MRI at SI joints and elevated CRP at baseline. The Applicant should consider other factors that may impact the effect of treatment, such as duration of disease and prior use of therapy. Additionally, the Applicant should develop and submit plans for risk mitigation and safe use of CZP in the targeted population.

3.2. Summary of Presubmission/Submission Regulatory Activity

A summary of interactions between the Applicant and the Agency preceding the original submission of Supplement 237 was provided in the clinical review by Dr. Janet Maynard. Table 3 below details the interactions following the Complete Response.

Table 3. Overview of Regulatory Interactions for nr-axSpA Development Program

Meeting Date	Type of Meeting	FDA Recommendations and Key Discussion Topics
September 23, 2014	Type C, Written Responses	• UCB proposed a new trial to address CR. o 48-Week, DB, PC study of CZP vs. PBO o 240 patients with nr-axSpA ▪ Back pain duration ≥ 1 year ▪ Failed ≥ 2 NSAIDs ▪ 2 subgroups: MRI+/CRP+ and MRI+/CRP- o Primary endpoint of ASAS40 at Week 12 • FDA expressed many concerns with proposal. o The study duration should be 52 weeks or longer. ▪ The Agency recommended that this could be accomplished by allowing Investigators to modify background medications. ▪ The Agency recommended against a formal escape. ▪ After discontinuation of study medications, patients should be considered non-responders. o The FDA noted that subgroups of ways patients could have objective inflammation were incomplete. UCB should also evaluate patients who are MRI-/CRP+. o Primary endpoint should be assessed at Week 52, e.g., a composite of those remaining in the study + ASAS40 at Week 52. o Primary and secondary endpoints should focus on signs and symptoms of axSpA disease activity.

March 26, 2015	Type C, Written Responses	• UCB proposed study AS0006 (see Section 8.1.1 for description of study).
		• The FDA did not have any major clinical concerns.
		  ○ No regulatory precedent for ASDAS-MI as the primary endpoint, but it appeared to be reasonable.
		  ▪ Agency noted that major secondary endpoints (specifically, ASAS40) should yield similar outcomes.
		  ▪ Results should not be driven by any 1 component of ASDAS-MI.
		  ▪ Primary and secondary endpoints should be evaluated at other time points, e.g., earlier time points when fewer patients may have modified background medications.
		  ○ ASAS/OMERACT definition of MRI+ appeared to be reasonable to use as inclusion criterion.
		  ○ Wording of indication will be a review issue.
		• FDA did provide some recommendations for the SAP.
		  ○ Agency recommended ways to minimize missing data.
		  ○ MMRM analyses for continuous key secondary endpoints were not acceptable.
		  ○ ANCOVA analysis of SI joint SPARCC socares was not acceptable.
		  ○ Sensitivity analyses (e.g., tipping point analyses) will be important if there are missing data at Week 52.
		  ○ Agency agreed that high PBO discontinuation due to lack of efficacy could potentially support the alternative hypothesis of a treatment difference.

November 17, 2017	Type C, Written Responses	• FDA did not agree with pooling data from AS0006 and AS001 for efficacy analysis of ASAS40 at Week 12. • Descriptive summary statistics and logistic regression for ASAS40 at Week 12 for various subgroups were reasonable. • FDA agreed with proposed data cut date for ongoing open-label studies (AS0005 and AS0007). • The Agency noted that safety data from AS001 (including open-label data through Week 204) may be reasonable to support long-term safety, but conclusions may be limited. • The Agency provided comments on pooling and planned analyses for safety, particularly in light of different treatment arms, follow-up times, and cross-over times. • FDA agreed that PK and ADA data from different studies should not be pooled.
May 24, 2018	FDA comments on SAP	FDA provided several comments on the SAP for AS0006.

		• For a labeling claim, AS-QoL PRO should be evaluated per the guidance. • Primary estimand should be evaluated according to ICH E9 (R1) guidance. • The LOCF sensitivity analysis for BASDAI and BASFI was not appropriate. • Recommendations regarding "observed case" analysis • Subgroup analyses of race, gender, and age should include treatment comparisons with corresponding confidence intervals. • Safety analyses of serious adverse events and adverse events of special interest should compare treatment groups with respect to risk. • Instead of performing analyses (MAR-based multiple imputation and tipping point) on each component of ASAS40 independently, Agency recommended performing analyses on the overall ASAS40 variable.

Abbreviations: SpA= spondyloarthritis; nr-axSpA= nonradiographic axSpA; NSAIDs=nonsteroidal anti-inflammatory drugs ; DB=double-blind;PC=placebo-controlled; CR=Complete Response; PBO=placebo; CZP=certolizumab pegol; SAP=statistical analysis plan; PK=pharmacokinetic; ADA=anti-CZP/anti-drug antibody; BASDAI= Bath Ankylosing Spondylitis Disease Activity Index; BASFI= Bath Ankylosing Spondylitis functional index; MAR=missing-at-random; ASAS20,ASAS40= Assessment of SpondyloArthritis International Society 20%, 40% response criteri; AS-QoL= Ankylosing Spondylitis-quality of life; PRO=patient reported outcomes; MMRM=mixed-effect repeated-measures model ; ANCOVA=analysis of covariance; SI=sacroiliac; SOARCC=Spondyloarthritis Research Consortium of Canada; OMERACT=Outcome Measures in Rheumatology Clinical Trials; MRI=magnetic resonance imaging; CRP=C-reactive protein; ASDAS-MI=Ankylosing Spondylitis Disease Activity Score major improvement
[Source: Clinical Reviewer]

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

4.1. Office of Scientific Investigations (OSI)

An OSI inspection was not deemed necessary for this supplemental BLA.

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an on-site inspection was not warranted. Because this is a priority review, there was insufficient time for the inspections to be completed. One of the site (b) (4) was also inspecte (b) (4) (b) (4) thus, the inspection falls within the surveillance interval. The inspection was classified as Voluntary Action Indicated (VAI) for failure to adhere to criteria for evaluating run acceptability in 2 runs. However, following that applicant's written response, OSIS recommended that all study data be accepted. Additionall (b) (4) (b) (4)

4.2. Product Quality

No new CMC information was submitted and was not required for the regulatory decision for this supplement. The relevant information was reviewed in the original BLA.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

No device or companion diagnostic issues are submitted for review in support of this supplement.

5 Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology and toxicology studies were conducted or required to support the regulatory decision for this supplement. The relevant information was previously reviewed in the original BLA.

6 Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology information of this sBLA consists of pharmacokinetic and immunogencity data collected from 2 phase 3 studies AS0006 and AS001. For details regarding the design of these studies see Section 7. The clinical pharmacology information from study AS001 was submitted during the previous submission (See clinical Pharmacology review in DARRTs dated 05/27/2013). A new bioanalytical methods for analyzing plasma CZP concentrations and ADA status were used in AS0006. Therefore, pooled analyses with AS001 were not performed. Clinical pharmacology information from studies AS0006 and AS001 are summarized below:

- The proposed dosing for non-radiographic axial spondyloarthritis is 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. The dosing regimen is acceptable as both doses have demonstrated clinical efficacy and tolerable safety profile (for details see Section 6.3 and Section 8 of the review) .
- The mean values for CZP trough at steady state ranged from 22.6 to 29.1 µg/mL for the 200 mg Q2W in study AS0006. The mean values for CZP trough at steady state ranged from 16.9 to 32.3 µg/mL and 12.2 to 18.7 µg/mL for the 200 mg Q2W and 400 mg Q4W in study AS001 (see Table 4 and Table 5).
- The CZP C_{trough} values for the 200 mg Q2W from studies AS0006 and AS001 were consistent.
- In study AS006, at the end of 52 week, 97.3% (248/255) of the patients in the treatment arm developed anti-drug antibodies. Of the patients classified as ADA positive, 22% (54/248) of patients developed neutralizing antibodies. ADA was measured using a new ECL based method which has greater sensistivity and higher tolerance compared to the previous assay. Therefore the ADA incidence from this study appears higher than previously reported values in study AS001 and the label. The new neutralizing antibody assay may not be sensitive to detect neutralizing antibody. Hence these numbers may be misleading and should be interpreted with caution. Please refer to OBP's separate review for detailed comments on the antibody measurement assay.
- The relative impact of ADA on PK and efficacy were inconclusive given the small number of patients who remained ADA negetive in the trial.
- In study AS001, at the end of 192 week, 5.8% (9/154) and 13.4% (21/157) of the patients in the treatment arm developed anti-drug antibodies in 200 mg Q2W and 400 mg Q4W, respectively. The overall incidence of ADA positive patients was 9.6% (30/311) in both the treatment arms. Neutralizing antibodies were not evaluated in AS001.
- For the AS001 study, efficacy was lower in the ADA positive patients than in the antibody negative patients. The percentage of ASAS20 responders at week 204 in the All CZP group was 33.3% in antibody positive patients and 53.3% in antibody negative patients. However,

due to the small number of patients who were ADA positive and limitations of the previous ADA assay, these results should be interpreted with caution.

Recommendation:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology II has reviewed the clinical pharmacology information submitted to sBLA125160/S-237. This sBLA is approvable, with the agreed upon labeling changes, from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The major clinical pharmacology findings of the current review are summarized in section 6.3.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing for non-radiographic axial spondyloarthritis is 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.

Therapeutic Individualization

None.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A new bioanalytical methods for analyzing plasma CZP concentrations and ADA status were used in AS0006. Therefore, pooled analyses with AS001 were not performed. Pharmacokinetic (PK) and immunogenicity data from AS0006 and AS001 for indivisual studies are summarized below.

Study AS0006:
Trough concentrations were collected in study AS0006 at 1, 2, 4, 12, 24, 36 and, 52 weeks. Immungencity samples were collected at 1, 2, 4, 12, 24, 36 and, 52 weeks. The time profile of plasma concentration for CZP is shown in Figure 2.

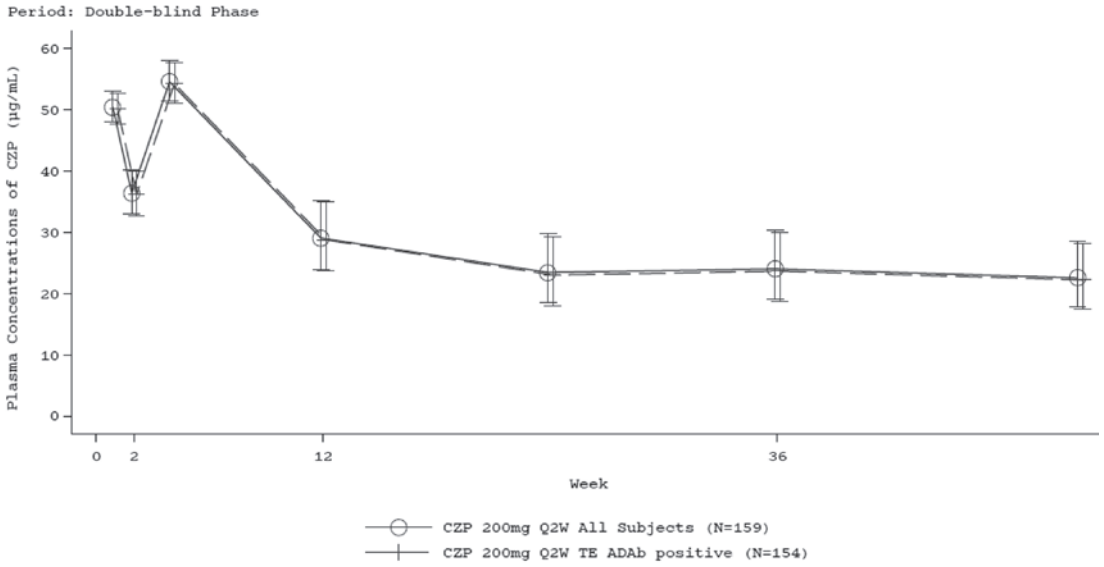
For all patients who were randomized to CZP 200 mg Q2W (n=159), the highest geometric mean CZP concentration (54.6 µg/mL) was observed at Week 4 (2 weeks after patients received the second loading dose of CZP 400mg), which subsequently decreased upon lowering the dose to CZP 200 mg Q2W, then remained generally stable through the 52-week treatment period. Similar CZP concentrations were observed for ADA positive patients (n=154) (Figure 2). Table 4 shows the concentration by time.

Table 4. CZP plasma concentration (µg/mL) by visit for CZP patients overall (SS)

Treatment	Visit, Week Number	n	Geo. Mean	95% CI of the geo. mean	Median	Min	Max	Geo. CV (%)
CZP 200mg Q2W, All Subjects N=159	V2, WK1	148	50.5	(48.0, 53.0)	51.8	16	92	31.42
	V3, WK2	153	36.4	(33.0, 40.1)	38.3	0	71	67.02
	V4, WK4	155	54.6	(51.4, 58.0)	56.7	4	135	39.58
	V8, WK12	143	29.1	(24.0, 35.2)	37.2	0	87	169.49
	V14, WK24	135	23.5	(18.5, 29.7)	31.8	0	68	245.51
	V20, WK36	123	24.0	(19.0, 30.4)	33.2	0	79	213.93
	V28, WK52	123	22.6	(17.8, 28.6)	31.9	0	70	221.01
CZP 200mg Q2W OL switchers N=20	OL CZP WK0	18	26.0	(21.0, 32.0)	27.7	8	55	44.43
	OL CZP WK4	19	49.4	(41.8, 58.4)	53.1	19	76	35.55
	OL CZP WK12	19	28.6	(23.4, 34.9)	33.2	13	52	43.17
	OL CZP WK24	15	24.9	(20.5, 30.3)	27.7	13	42	36.40
	OL CZP WK36	6	8.9 [a]	(0.3, 232.3)	30.6	0	39	12421.22

[Source: Summary of Clinical Pharmacology, Table 2.1, page 10]

Figure 2. Geometric mean (95% CI) of CZP plasma concentration (µg/mL) versus scheduled time during the Double-Blind Treatment Period of AS0006 (SS)

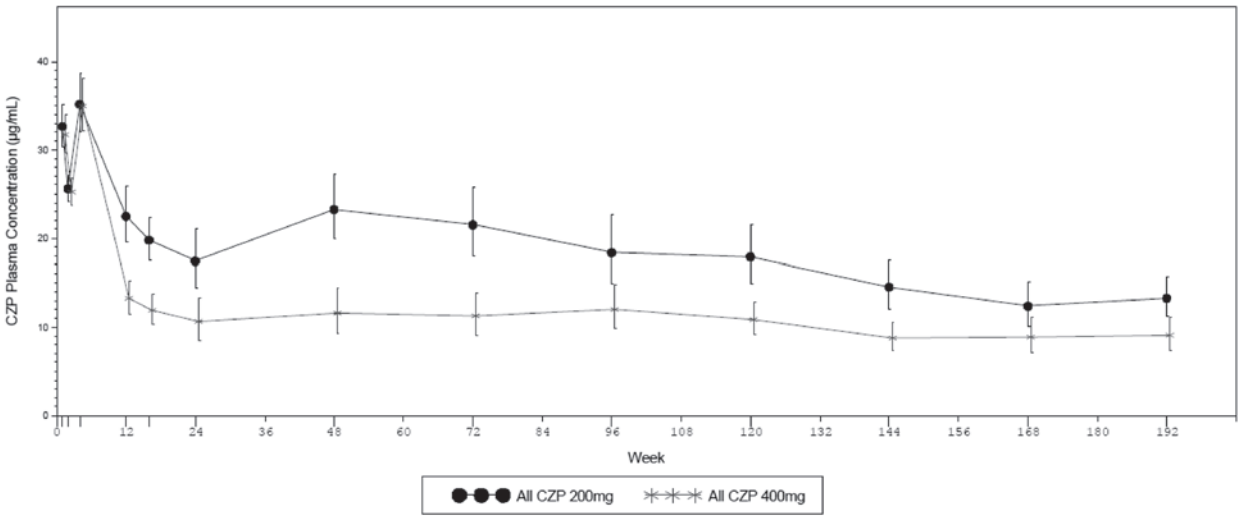


[Source: Summary of Clinical Pharmacology, Figure 2.1, page 13]

Study AS001:

Trough concentrations were collected in study AS001 at 1, 2, 4, 12, 16, 24, and thereafter every 24 weeks until the Safety Follow-Up Visit (10 weeks after the last dose of study medication). Immungencity samples were collected at baseline and weeks 1, 2, 4, 12, 16, 24, and thereafter every 24 weeks until the Safety Follow-Up Visit. The time profile of plasma concentration for CZP in the 200 mg Q2W and 400 mg Q4W arms are shown in Figure 3. and summarized in Table 5. The exposure was lower in the 400 mg Q4W regimen compared to the 200 mg Q2W regimen. However, these differences did not translate into clinically meaningful differences between the two dosing regimens based on the available efficacy comparisons, as described in Section 8.1. The ASAS40 response was similar for both doses of CZP (30.3% on 200 mg Q2W and 36.7% on 400 mg Q4W). The plasma concentration by ADA status is shown in Figure 4.

Figure 3. Geometric mean (±95% CI) CZP plasma trough concentrations (µg/mL) - actual values by visit – overall axSpA population (PK PPS [OC])-AS001



[Note: CZP 200 mg dose was administered as every 2 weeks (Q2W-Black); CZP 400 mg dose was administered as every 4 weeks (Q4W-Red), Source: AS001 Final CSR figures, Figure 2.1.1, page 15, Summary of Clinical Pharmacology, Figure 2.4, page 24]

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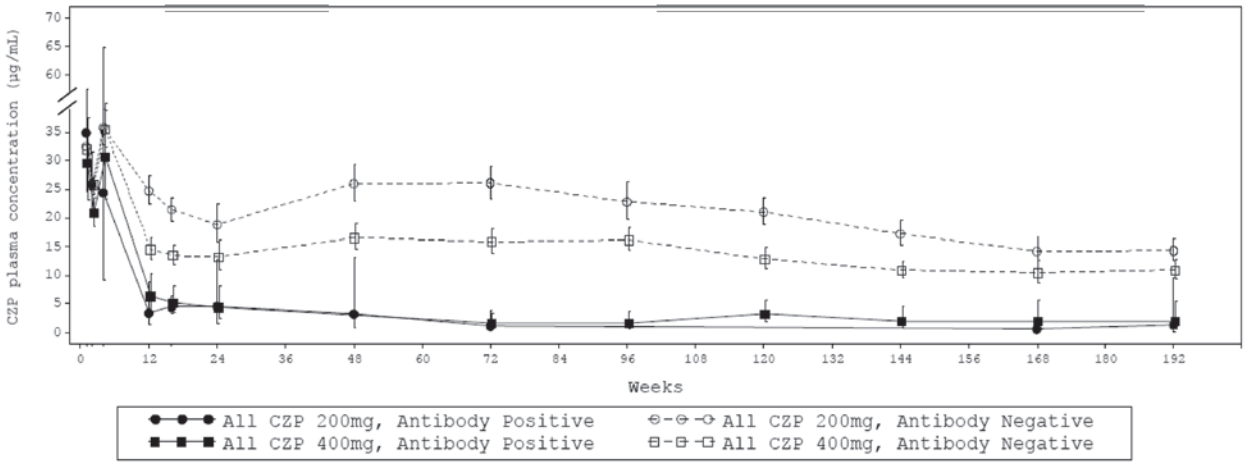
Table 5. CZP plasma trough concentrations (µg/mL) at steady state from Week 24 through week 192

Study week	Wk0 CZP 200mg Q2W N=108	Wk0 CZP 400mg Q4W N=107	Wk0 All CZP N=215	All CZP 200mg Q2W N=154	All CZP 400mg Q4W N=157	All CZP N=311
Week 24, n	62	54	116	74	72	146
Geo. mean (CV%)	17.00 (45.52)	10.36 (72.18)	13.50 (58.63)	17.43 (49.89)	10.61 (67.67)	13.64 (60.11)
Mean (SD)	20.69 (9.42)	13.66 (9.86)	17.42 (10.21)	21.28 (10.62)	14/27 (9.66)	17.82 (10.71)
Min, max	BLQ, 47.9	BLQ, 58.2	BLQ, 58.2	BLQ, 62.6	BLQ, 58.2	BLQ, 62.6
Week 48, n	92	84	176	132	124	256
Geo. mean (CV%)	26.23 (52.12)	12.70 (68.75)	18.55 (63.92)	23.26 (55.61)	11.55 (69.85)	16.57 (66.23)
Mean (SD)	32.25 (16.81)	18.67 (12.83)	25.77 (16.47)	29.93 (16.65)	17.80 (12.43)	24.06 (15.93)
Min, max	BLQ, 80.1	BLQ, 59.5	BLQ, 80.1	BLQ, 80.1	BLQ, 59.5	BLQ, 80.1
Week 96, n	85	80	165	124	119	243
Geo. mean (CV%)	19.66 (55.36)	13.97 (58.09)	16.66 (59.69)	18.36 (55.50)	12.03 (63.74)	14.93 (62.49)
Mean (SD)	26.74 (14.80)	18.61 (10.81)	22.80 (13.61)	26.08 (14.47)	17.27 (11.01)	21.76 (13.60)
Min, max	BLQ, 65.4	BLQ, 60.7	BLQ, 65.4	BLQ, 65.4	BLQ, 60.7	BLQ, 65.4
Week 144, n	81	78	159	115	110	225
Geo. mean (CV%)	14.91 (54.59)	9.46 (58.26)	11.93 (61.38)	14.56 (53.18)	8.79 (59.63)	11.37 (61.35)
Mean (SD)	19.73 (10.77)	12.33 (7.18)	16.10 (9.88)	19.36 (10.30)	11.81 (7.04)	15.67 (9.61)
Min, max	BLQ, 48.7	BLQ, 40.6	BLQ, 48.7	BLQ, 48.7	BLQ, 40.6	BLQ, 48.7
Week 192, n	68	72	140	97	99	196
Geo. mean (CV%)	14.18 (47.46)	8.70 (60.76)	11.03 (55.48)	13.32 (48.42)	9.04 (59.40)	10.95 (54.84)
Mean (SD)	16.84 (7.99)	12.19 (7.41)	14.45 (8.02)	16.25 (7.87)	12.36 (7.34)	14.28 (7.83)
Min, max	BLQ, 41.4	BLQ, 32.1	BLQ, 41.4	BLQ, 41.4	BLQ, 36.8	BLQ, 41.4

[Note: Patients who received placebo during the double-blind treatment period and switched to CZP 200mg Q2W or CZP 400mg Q4W at Weeks 16 or 24 are included in the All CZP treatment groups. Source: Summary of Clinical Pharmacology, Table 2.6, page 23]

Figure 4. Geometric mean (±95% CI) CZP plasma trough concentrations (µg/mL) - actual values by visit by ADA status – overall axSpA population in AS001 (PK-PPS [OC])



[Note: CZP 200 mg dose was administered as every 2 weeks (Q2W); CZP 400 mg dose was administered as every 4 weeks (Q4W), Source: AS001 Final CSR figures, Figure 2.2.1, page 18, Summary of Clinical Pharmacology, Figure 2.5, page 28]

6.3.2. Clinical Pharmacology Questions

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing for non-radiographic axial spondyloarthritis is 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.

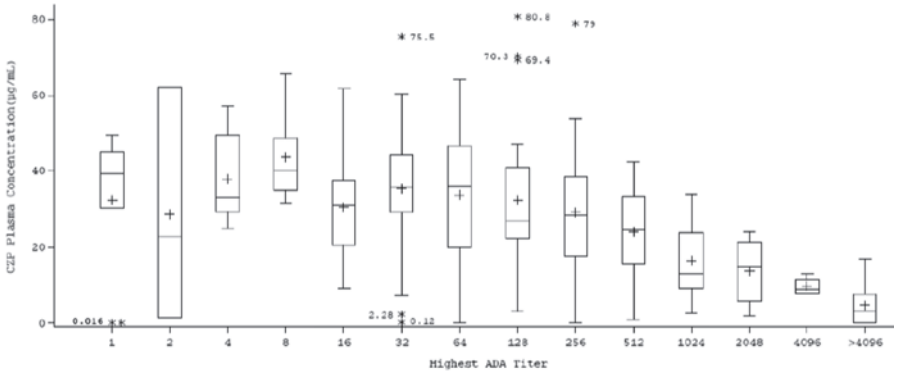
Clinical efficacy of the proposed dosing regimens are demonstrated in studies AS0006 and AS001. The overall safety profiles were comparable with the known safety profile of certolizumab pegol. Refer to Section 8 for more details.

What is the incidence of the formation of ADA and the impact of immunogenicity on certolizumab pegol exposure, efficacy and safety?

ADA impact on PK:
In AS0006, 97.3% (248/255) of patients became ADA positive during the 52-week treatment period using the new ECL assay with more sensitivity. Given the high number of patients who are ADA positive (97.3%), it was not meaningful to compare PK, efficacy, and safety between ADA-positive and ADA-negative patients.

The high ADA titer group had lower CZP plasma trough concentrations. In patients with an ADA titer ≥1024 (10.7%, 17 of 159 patients) there appeared to be a trend towards lower CZP concentration with increasing titer (Figure 5).

Figure 5. Box and whiskers plot of CZP plasma concentration (µg/mL) by highest Individual ADA tier in AS0006 (SS)



[Source: Summary of clinical pharmacology, Figure 2.2, page 15, AS0006 Interim CSR Figure 2.9, page 285]

In AS001, the majority of patients (90.4% [281/311]) were ADA negative during the study; only 9.6% (30/311) of patients were ADA positive at any time during the study (through Week 192). It was observed that patients who were detected to be ADA positive had lower CZP concentrations compared to patients who remained ADA negative during the study (Figure 4 and Table 6).

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Table 6. Anti-CZP antibody status through Week 192 – overall axSpA population in AS001 (SS)

Study week	Wk0 CZP 200mg Q2W N=111 n/Nobs (%)	Wk0 CZP 400mg Q4W N=107 n/Nobs (%)	Wk0 All CZP N=218 n/Nobs (%)	All CZP 200mg Q2W N=158 [a] n/Nobs (%)	All CZP 400mg Q4W N=157 [a] n/Nobs (%)	All CZP N=315 [a] n/Nobs (%)
Any time during the study						
Positive	6/108 (5.6)	11/107 (10.3)	17/215 (7.9)	9/154 (5.8)	21/157 (13.4)	30/311 (9.6)
Negative	102/108 (94.4)	96/107 (89.7)	198/215 (92.1)	145/154 (94.2)	136/157 (86.6)	281/311 (90.4)
Baseline						
Positive	0/96	0/99	0/195	0/136	0/145	0/281
Negative	96/96 (100)	99/99 (100)	195/195 (100)	136/136 (100)	145/145 (100)	281/281 (100)
Week 24						
Positive	3/63 (4.8)	4/55 (7.3)	7/118 (5.9)	3/75 (4.0)	4/73 (5.5)	7/148 (4.7)
Negative	60/63 (95.2)	51/55 (92.7)	111/118 (94.1)	72/75 (96.0)	68/73 (94.5)	141/148 (95.3)
Week 48						
Positive	4/92 (4.3)	7/85 (8.2)	11/177 (6.2)	4/132 (3.0)	13/126 (10.3)	17/258 (6.6)
Negative	88/92 (95.7)	78/85 (91.8)	166/177 (93.8)	128/132 (97.0)	113/126 (89.7)	241/258 (93.4)
Week 96						
Positive	4/85 (4.7)	7/80 (8.8)	11/165 (6.7)	7/124 (5.6)	14/119 (11.8)	21/243 (8.6)
Negative	81/85 (95.3)	73/80 (91.3)	154/165 (93.3)	117/124 (94.4)	105/119 (88.2)	222/243 (91.4)
Week 144						
Positive	4/81 (4.9)	9/78 (11.5)	13.159 (8.2)	6/115 (5.2)	14 /109 (12.8)	20/224 (8.9)
Negative	77/81 (95.1)	69.78 (88.5)	146/159 (91.8)	109/115 (94.8)	95/109 (87.2)	204/224 (91.1)
Week 192						
Positive	2/68 (2.9)	7/72 (9.7)	9/140 (6.4)	3/97 (3.1)	11/99 (11.1)	14/196 (7.1)
Negative	66/68 (97.1)	65/72 (90.3)	131/140 (93.6)	94/97 (96.9)	88/99 (88.9)	182/196 (92.9)

[Note: Patients who received placebo during the double-blind treatment period and switched to CZP 200mg Q2W or CZP 400mg Q4W at Weeks 16 or 24 are included in the All CZP treatment groups. Source: Summary of Clinical Pharmacology, Table 2.8, page 30]

ADA impact on Efficacy:
In AS0006, the relative impact of ADA on PK and efficacy were inconclusive given the small number of patients who remained ADA negative in the trial.

In AS001, efficacy was lower in the ADA positive patients than in the antibody negative patients. The percentage of ASAS20 responders at Week 204 in the All CZP group was 33.3% in antibody positive patients and 53.3% in antibody negative patients. However, due to the small number of patients who were ADA positive and limitations of the previous ADA assay, these results should be interpreted with caution.

ADA impact on Safety:
In AS0006, 97.3% of patients became ADA positive during the 52-week treatment period, using the more sensitive analytical method. Given the number of patients with ADA positivity, it was not meaningful to compare ADA-positive and ADA-negative patients.

In AS001, 9.6% of patients became ADA positive during the study. The Applicant states that number of patients were too small to draw any meaningful conclusions about the impact of antibody positivity on adverse events.

Are the bioanalytical methods properly validated to measure PK in plasma samples?
Yes. For AS0006 study, plasma CZP concentrations were measured using a newly developed more sensitive electrochemoluminescence (ECL) assay.

Briefly, CZP is captured by recombinant human TNFα which is coated onto a 96 we (b) (4) standard bind plate. Following a wash step to remove any unbound capture reagent, the plate is blocked using Assay Diluent (0.5% skimmed milk powder in Assay Buffer) for 1 hour. Following a wash step, samples, calibrators, and quality controls (QCs) were incubated using a minimal required dilution (MRD) of 1/100 for 1 hour. Certolizumab pegol in the samples, calibrators, and QC samples will bind to the TNFα bound to the plate and any unbound substances were washed off. The primary detection reagent, a rabbit anti-PEG conjugated to biotin was added and subsequently any unbound detection reagent was washed off. The secondary detection reagent, streptavidin-SulfoTAG causes a luminescence signal emission when an ECL substrate is added and the current applied to the electrodes built into th (b) (4) plate. The analyte concentration of unknown samples is determined by comparison against a standard curve. The LLOQ of the assay was determined to be 0.032µg/mL. The major assay validation parameters for new ECL assay are summarized in
Table 7 below.

Table 7. Summary of the validation of the methods to determine CZP concentrations in human lithium heparin plasma

Bioanalytical Method	ELISA	ECL assay
Bioanalytical method validation reports	Ligand binding assay with colorimetric readout: (b) (4) (b) (4) Method Validation Report 7213-110, Method Validation Report 7213-110 Addendum 1, and Method Validation Report 7213-110 Addendum 2	Ligand binding assay with ECL readout on (b) (4) (b) (4) Method Validation Report NCD2961
Method reference	ELISA-0168	(b) (4) 4056
Test reference standard	Test article CZP (Lot # B093676)	Test article CZP (CDP870-RS-002)
Method used in studies	AS001	AS0006
Analyte	CZP	CZP
Sampling matrix	Lithium heparin plasma	Lithium heparin plasma
Calibration range	0.412 to 33.3µg/mL	0.032 to 5.00µg/mL
Within run precision (% CV)	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	≤ 9.10%
Between run precision (% CV)	6.10% to 10.8% for QC levels (32.5% at LLOQ)	≤ 5.0% for QC levels
Within run accuracy (% AR)	98.2% to 105% for QC levels (66.6% at LLOQ)	92.5 to 116.6% for QC levels (130.3% at LLOQ)
Between run accuracy (% AR)	96.8% to 105% for QC levels (66.6% at LLOQ)	98.8 to 106.0% for QC levels
Total error (%)	65.9% (LLOQ); 11.4% (ULOQ)	≤ 13.7% for QC levels
Sample processing stability	48 hours at room temperature	25 hours at room temperature
Long-term stability	772 days at -60°C to -80°C	182 days at -20°C to -80°C [a]
Freeze/thaw stability	Up to 9 freeze/thaw cycles	14 cycles from nominally -80°C, 9 cycles from nominally -20°C
Dilution linearity	Samples up to 200µg/mL can be tested	Up to 500 times dilution
Selectivity in plasma from subjects with nr-axSpA	Not tested	Selectivity demonstrated at LLOQ and ULOQ level

[Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 1.2, pages 5-6]

The older enzyme-linked-immunosorbent assay (ELISA) method was used in the AS001 study, which supported the initial axSpA (including ankylosing spondylitis and nr-axSpA) sBLA filing and has been reviewed earlier. Table 8 shows the differences between the older ELISA assay and newly developed ECL assay.

Table 8. Summary of the differences in the methodologies for the PK and CZP anti-antibody assays for AS001 and AS0006

Study number	AS0006	AS001
	PK assay	
Format	ECL assay measuring total active drug	Sandwich ELISA measuring total active drug
Dynamic range (µg/mL)	0.032 to 5.00	0.412 to 33.3
	ADAb assay	
Format	ECL-based homogenous bridging assay	ELISA-based sequential bridging assay
Positive Control Material	Rabbit monoclonal anti-idiotypic Ab	Affinity-purified rabbit anti-CZP polyclonal antiserum
Sensitivity	100ng/mL	>600ng/mL
Drug Tolerance – positive control	PC of 100ng/mL can still be detected in presence of drug concentrations up to 100µg/mL	Not tested

(Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 1.1, page 4)

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 9. Clinical Trials Supporting BLA 125160 Supplement 237

Trial Identity Study Center and Countries Status	Trial Design/Treatment Duration/Follow-Up	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population
Controlled Studies to Support Efficacy and Safety					
AS0006 104 centers Australia, Bulgaria, Canada, Czech Republic, Hungary, Poland, Russian Federation, Taiwan, US *Ongoing*	Phase 3, multicenter study consisting of 2 analysis periods to evaluate the efficacy, safety, and tolerability of CZP in patients with active axSpA: • Double-blind period: Randomized, double-blind, placebo-controlled study for 52 weeks Safety follow-up (SFU) period for 10 weeks after last dose • Open-label Safety Follow-up Extension (SFE) period: uncontrolled 2-year period	Double-blind period: CZP 200mg SC Q2W (loading dose 400mg at Weeks 0, 2, 4) or PBO SC Q2W Escape: CZP 200mg Q2W or other treatment Open-label SFE: CZP 200 mg Q2W	Primary: ASDAS-MI at Week 52 Secondary: • ASAS40 at Wks 12 and 52 • Change from baseline - BASFI - BASDAI - SPARCC score - ASQoL - NRS • Anterior uveitis flares • Change in background meds	317 patients randomized CZP: 159 patients PBO: 158 patients 285 patients completed Week 52	Patients with active axSpA without x-ray evidence of AS and with objective signs of inflammation (sacroiliitis on MRI and/or elevated CRP)

AS001 128 centers Argentina, Belgium, Brazil, Canada, Czech Republic, France, Germany, Hungary, Italy, Mexico, the Netherlands, Poland, Spain, UK, US *Complete*	Phase 3, multicenter study consisting of 3 analysis periods to assess efficacy, safety, and tolerability of CZP in patients with active axSpA: • Double-blind period: Randomized, double-blind, parallel-group, placebo-controlled study for 24 weeks • Dose-blind period: Uncontrolled for 24 weeks • Open-label period: Uncontrolled for 156 weeks SFU period for 10 weeks after last dose	• Double-blind period: CZP 200mg SC Q2W or CZP 400mg SC Q4W (loading dose 400mg at Weeks 0, 2, 4) or PBO Escape: CZP 200mg Q2W or CZP 400mg Q4W (loading dose 400mg at Weeks 0, 2, 4) • Dose-blind period: CZP 200mg Q2W or CZP 400mg Q4W • Open-label period: CZP 200mg Q2W or CZP 400mg Q4W	Primary: ASAS20 at Week 12 Key Secondary: • ASAS20 at Wk 24 • Change from baseline - BASFI - BASDAI - BASMI - ASspiMRI-a - SPARCC	325 patients randomized CZP 200mg: 111 patients CZP 400mg: 107 patients PBO: 107 patients	Patients active axSpA (including AS and nr-axSpA) Safety analysis for this supplement: only nr-axSpA patients with objective signs of inflammation are included
Studies to Support Safety					
AS0005 Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, the Netherlands, Poland, Romania, Spain, Taiwan, Turkey,	Phase 3b, multicenter study consisting of 2 analysis periods to assess efficacy, safety, and tolerability of CZP in patients with active axSpA who achieve sustained remission in Part A and to assess efficacy, safety, and tolerability of CZP and maintenance of remission in Part B after withdrawing or reducing the dose:	• Part A: CZP 200mg SC Q2W (loading dose 400mg at Weeks 0, 2, 4) • Part B: CZP 200mg Q2W or CZP 200mg Q2W or PBO Escape: CZP 200mg Q2W		736 patients enrolled	Patients with axSpA (including AS and nr-axSpA) Safety analysis for this supplement: only nr-axSpA patients with objective signs of inflammation are included

UK, US *Ongoing* Safety data cut on Feb 19, 2018	• Part A: Open-label run-in period for 48 weeks • Part B: Randomized, double-blind, parallel-group, placebo-controlled period for 48 weeks SFU period for 10 weeks after last dose				
AS0007 Czech Republic, Germany, Poland, Spain, the Netherlands *Ongoing* Safety data cut on Feb 19, 2018	Phase 4 multicenter, open-label study for 96 weeks to assess the efficacy and safety of CZP treatment on the reduction of anterior uveitis (AU) flares in patients with both active axSpA and a documented history of AU SFU period for 10 weeks after last dose	CZP 200mg SC Q2W (loading dose 400mg at Weeks 0, 2, 4)		86 patients enrolled	Patients with axSpA (including AS and nr-axSpA) and a history of AU Safety analysis for this supplement: only nr-axSpA patients with objective signs of inflammation are included

7.2. Review Strategy

The primary evidence of efficacy to support the 200 mg SC Q2W doing are derived from study AS0006. Data from the nr-axSpA population in study AS001 provide supportive efficacy data, and efficacy data to support the CZP 400 mg Q4W chronic dosing regimen. AS001 was reviewed in detail during the first review cycle for Supplement 237. Thus, references will be made to the original review.

The majority of the safety assessment is also based on study AS0006 along with the nr-axSpA population from AS001. Additionally, supportive safety data, particularly for AEs of special interest, will be obtained from ongoing studies AS0005 and AS0007. Details of the pooled safety databases are provided in Section 8.2.

The statistical reviewer will review the Applicant's assessment of efficacy as well as supplement the Applicant's analyses with his own analysis.

The clinical reviewer will present the Applicant's safety data with additional commentary.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. AS0006

Trial Design

Basic Study Design

Study AS0006 was a 52-week, multicenter, randomized, double-blind, parallel group, placebo-controlled clinical study to evaluate the efficacy and safety of CZP in adult patients with active axSpA without x-ray evidence of AS and with objective signs of inflammation (sacroiliitis on MRI and/or elevated CRP) and who had an inadequate response to, had a contradiction to, or were intolerant to NSAIDs. After the Week 52 Visit assessment, eligible patients could receive open-label (OL) CZP treatment for an additional 2 years in the OL Safety Follow-Up Extension (SFE). Figure 6 presents the study design of AS0006 as a schematic diagram.

The study was comprised of 3 periods.

- **Period 1 (Screening Period):** Up to 6 weeks before Baseline

- **Period 2 (Double-Blind Period):** Week 0 to Week 52, placebo-controlled

Eligible patients were randomized 1:1 to the following double-blind study treatments:

- CZP 400mg administered at Weeks 0, 2, and 4, followed by CZP 200mg Q2W (starting at Week 6 up to and including Week 50)
- Placebo

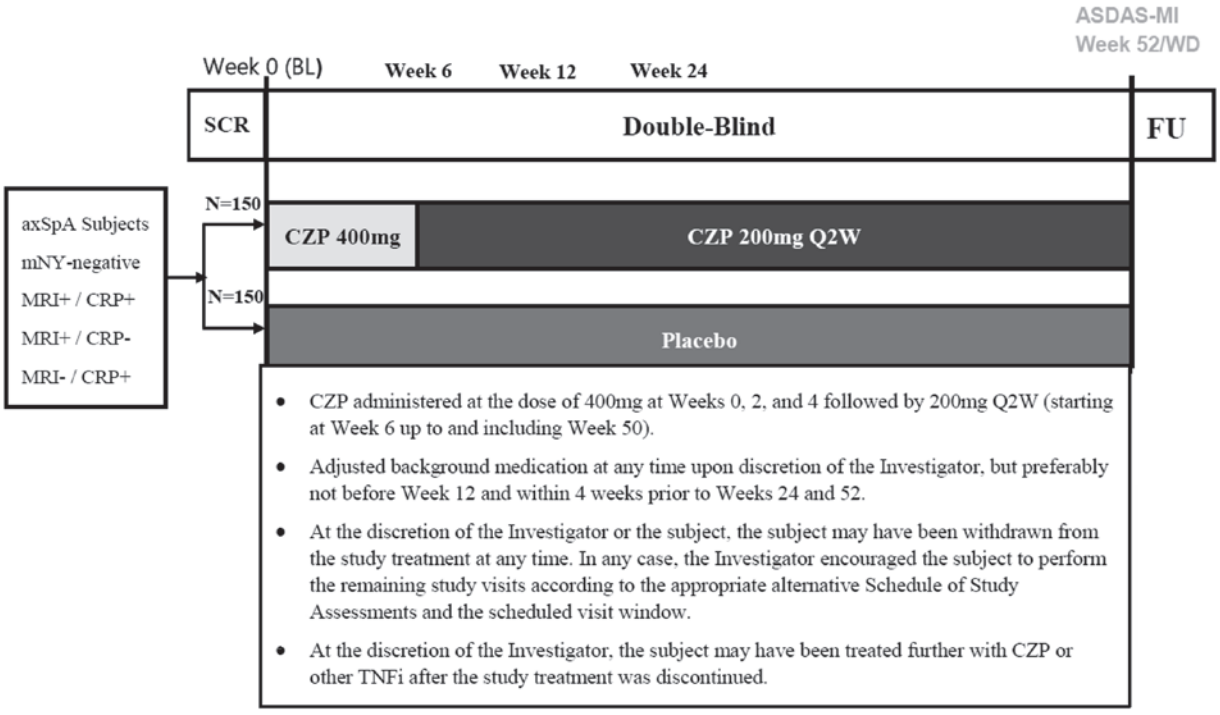
Alternative schedules: Patients were permitted to switch from double-blind study treatment to OL CZP or alternative treatment at any time. Patients who discontinued the double-blind study treatment and entered OL treatment with CZP were assessed two and four weeks after initiation of OL CZP treatment and every 12 weeks thereafter. Alternatively, patients who discontinued the double-blind study treatment and received other treatment were assessed every 12 weeks after initiation of other treatment.

For either treatment schedule, assessments were to be conducted until as close as possible to Week 52.

- **Period 3 (Follow-Up Period):** All patients no participating in the SFE period after Week 52 had a follow-up visit 8 weeks after the Week 52 or Withdrawal (WD) visit.

- **SFE Period:** Week 52 to Week 156, OL
  After the Week 52 visit assessments, patients on double-blind study treatment could receive OL CZP for an additional 2 years. Patients who withdrew from double-blind study treatment but were transitioned to OL CZP were also eligible to enter the SFE Period. Patients on alternative treatments could not participate in the SFE Period.

Figure 6. Study AS0006 Schematic Diagram



[Source: UCB, AS0006 Interim Clinical Study Report, Figure 3-3. Dated Sep 24, 2018: page 66.]

Key Inclusion Criteria

- Patients must have had a documented diagnosis of adult-onset axSpA and have met ASAS criteria for axSpA (not including family history and good response to NSAIDs). See Section 2.1 for details regarding ASAS criteria.
- Patients must have had back pain for at least 12 months before Screening.
- Patients must NOT have had sacroiliitis defined by mNY critiera (bilateral ≥ Grade 2; unilateral ≥ Grade 3) on SI joint x-rays (based on central readings of x-rays) within the last 12 months from Baseline. See Section 2.1 for further details regarding the mNY criteria.
    - If eligible patients did not have a suitable SI joint x-rays, then they underwent the x-ray during the Screening Period.
    - Confirmed mNY-negative axSpA patients then underwent MRI during the Screening Period, which was also centrally read. See below.
- Patients must have had a combination of current evidence of sacroiliitis on the screening MRI as defined by ASAS/Outcome Measures in Rheumatology Clinical Trials (OMERACT) scoring confirmed via central reading (MRI+) and CRP either >ULN or ≤ULN (for CRP, the ULN is defined as the ULN indicative for inflammatory disease) at Baseline (CRP+ or CRP-) OR no evidence of sacroiliitis on the screening MRI (MRI-) and CRP>ULN (CRP+) as follows:
    - MRI+/CRP+
    - MRI+/CRP-
    - MRI-/CRP+

  UCB noted that these 3 subgroups encompassed the nr-axSpA patient population that

would benefit most from anti-TNF therapy.

ASAS/OMERACT definition of MRI+ for sacroiliitis: the presence of bone marrow edema (BMO) or osteitis that is highly suggestive of SpA and located in the typical anatomical areas (subchondral or periarticular bone marrow). MRI+ is further defined as either >1 BMO lesion on one slice or a lesion that is present on at least 2 consecutive slices.

- Patients must have had active disease as defined by each of the following at Screening and Baseline:
    - BASDAI score ≥ 4
    - Spinal pain ≥ 4 on a 0 to 10 NRS (from BASDAI item 2)
- Patients must have had an inadequate response to, had a contraindication to, or been intolerant to at least 2 NSAIDs. Inadequate response to an NSAID was defined as lack of response to at least 14 days of routine NSAID therapy at the highest tolerated dose.

Key Exclusion Criteria

AxSpA-disease-related Exclusions:

- Patients must not have had AS or any other inflammatory arthritis from another diagnosis.
- Patients must not have had fibromyalgia.
- Patients must not have had a secondary, noninflammatory condition (e.g., osteoarthritis) that, in the Investigator's opinion was symptomatic enough to interfere with evaluation of the effect of study treatment on the patient's primary diagnosis of axSpA.

Medical History Exclusions:

- Female patients who were breastfeeding, pregnant, or planning to become pregnant during the study or within 3 months following the final dose of the investigational product
- Infection-related
    - Patients with a history of chronic/recurrent infections or recent serious/life-threatening infection (including hospitalization for infection) within the 6 months prior to the Baseline visit
    - Patients with a history of herpes zoster infection within 6 months prior to Baseline visit
    - Patients with known tuberculosis (TB) infection, at high risk of acquiring TB infection, or latent TB infection (LTBI) were excluded. Of note, patients with LTBI were allowed if they received appropriate prophylaxis prior to study treatment and continued prophylaxis to completion.
    - Patients with concurrent acute or chronic viral hepatitis B or C or with human immunodeficiency virus (HIV) infection
    - Patients with history of or current active infection with Histoplasma, Coccidiodes, Paracoccidiodes, Pneumocystis, nontuberculous mycobacteria, Blastomyces, or Aspergillus.
    - Patients must not have had a history of an infected joint prosthesis at any time.

  - Patients that received any live (including live attenuated) vaccination within 8 weeks prior to Baseline
  - Patients who had a high risk of infection in the Investigator's opinion. These could be patients with leg ulcers, with indewelling urinary cathether, permanently bedridden or wheelchair bound, etc.
- Malignancy-related
  - Patients with a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease
  - Concurrent malignancy or history of malignancy. Patients with <3 excised basal cell carcinomas or with cervical carcinoma in situ staus post successful surgical treatment >5 years prior to Screening could have been included.
- Patients with Class III or IV congestive heart failure per New York Heart Association 1964 criteria
- Patients with a history of, or suspected, demyelinating disease of the central nervous system (e.g., multiple sclerosis or optic neuritis)
- Patients having had major surgery (including joint surgery) within 8 weeks prior to Screening, or having planned surgery within 6 months after entering the study
- Patients with a current or recent history, as determined by the Investigator, of severe, progression, and/or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, or neurological disease
- Patients with significant laboratory abnormalities, including but not limited to the following:
  - Liver associated enzymes > 2x ULN
  - Estimated Glomerular Filtration Rate as measured by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) < 60 mL/min/1.73m^2
  - White blood cell (WBC) < 3.0 x 10^9/L

<u>Concomitant and Rescue Medication</u>
There was not a mandatory escape arm for placebo patients. Instead, Investigators could modify background medications advocated by treatment guidelines (NSAIDs, corticosteroids, analgesics, and slow-acting antirheumatic drugs) during the course of the study. If the Investigator determined that a patient's disease activity required escalation treatment with other medicines (including biologics), the study treatment could be discontinued, and patients could switch to OL CZP or other treatments.

All medications, including over-the-counter products, nutraceuticals, or herbals, that were used at any time during the course of the study were recorded in the clinic chart (source documentation) and the eCRF. Permitted concomitant medications were to remain stable for at least 4 weeks prior to Weeks 12, 24, and 52/Withdrawal assessments. Changes in permitted medications could be made according to the table below, but no changes were recommended in the first 12 weeks of the study. Table 10 describes concomitant medications that were both permitted and prohibited.

Table 10. Concomitant Medications

Drug class	Dose	Exclusion Criteria	Study Visits
Analgesics (e.g., acetaminophen, opiates, or combinations)	Up to maximum approved dose	Any change in stable dose regimen was excluded in the 14 days prior to the Baseline visit.	• Any prn use of analgesics was not permitted within 24 hours prior to any post-Screening visit. • An increase or addition in opiates or a combination with opiates was not recommended between Week 0 and Week 12 or within 4 weeks prior to the Week 24 or Week 52 visits.
NSAIDs (including COX-2 inhibitors)	Up to maximum approved dose regimen	Any change in stable dose regimen was excluded in the 14 days prior to the Baseline visit	• Any prn use of NSAIDs was not permitted within 24 hours prior to any post-Screening visit. • Changes in NSAID doses were to be avoided between Week 0 and Week 12 or within 4 weeks prior to the Week 24 or Week 52 visits.
Corticosteroids (po)	Maximum allowed ≤ 10mg daily total prednisone equivalent	Any change in stable dose used for axSpA in the 28 days prior to the Baseline visit. If a taper of oral corticosteroids was planned, this was to be completed 14 days prior to the Baseline visit.	• Maximum allowed ≤ 10mg daily total prednisone equivalent • Changes in dose or initiation of corticosteroids (including tapers) were to be avoided between Week 0 and Week 12 or within 4 weeks prior to the Week 24 or Week 52 visits.
Corticosteroids (im)	Any dose	Used in the 28 days prior to the Baseline visit	Corticosteroids (im) were not to be used during the study.
Corticosteroids (ia)	Up to maximum approved dose	Used in the 28 days prior to the Baseline visit	• SI joint corticosteroid (ia) injections were not allowed during the study. • Peripheral joint injections were permitted.
Corticosteroids (iv)	Up to maximum approved dose	Used in the 28 days prior to the Baseline visit	Doses of corticosteroids (iv) could have been used during the study for acute illnesses as long as the dose was not administered within 1 week prior to Weeks 12, 24, or 52 and as long as the underlying disease did not present a contraindication to the patient remaining in the study. Permitted indications included dermatitis,

			gastroenteritis, asthma, and pneumonia.
Hyaluronic acid (ia)	Any dose	Used in the 28 days prior to the Baseline visit	Used in the knee as needed after Week 12 visit
SSZ and/or HCQ and/or MTX and/or LEF and/or AZA	Maximum allowed: • SSZ ≤3g/day • HCQ ≤400mg/day • MTX ≤25mg/week • AZA ≤150mg/day • LEF ≤20mg/day	Initiation and/or any change in the dose in the 28 days prior to the Baseline visit	• Changes in doses were not to be made between Week 0 and Week 12 or within 4 weeks prior to the Week 24 or Week 52 visit. • Dose reduction to manage intolerance or safety issues was allowed at any time during the study, at the Investigator's discretion.
CYC, CTX, MMF apremilast	Up to maximum approved dose	Used within 28 days prior to the Baseline visit	Initiation or change in dose was to be avoided between Week 0 and Week 12 or within 4 weeks prior to Week 24 or Week 52 visit.
Anti-TNF therapies (IFX, ADA, ADA, ETN, GOL, CZP)	Any dose	Only 1 previous biologic was allowed. • For IFX, ADA, and GOL, any use within 3 months prior to the Baseline visit • For ETN, use within 28 days prior to the Baseline visit • For CZP any exposure history	If biologic therapy was required, the patient must have been discontinued from study treatment and should have conducted the remaining visits according to the alternative schedule.
Other rheumatologic therapies: ABA, RTX, anti-IL17, TCZ, UST, TOF, biosimiliar to any approved biologic	Any dose	Any exposure history	If other rheumatologic therapies were required, the patient should have been discontinued from study treatment and should have conducted the remaining visits according to the alternative schedule.
Osteoporosis medications, e.g., bisphosphonates (oral), denosumab, cathepsin K inhibitor,	Up to maximum approved dose	All stable osteoporosis medications were permitted except for iv bisphosphonates.	Osteoporosis medications with the exception of iv bisphosphonates were allowed without restriction.

cinacalcet, calcitonin			
IV bisphosphonates, e.g., zoledronic acid, ibandronate, pamidronate	Any dose	• Zoledronic acid: any use within the 3 years prior to randomization • Ibandronate or pamidronate: any use within the past 2 years	If iv bisphosphonates were initiated during the study, the patient should have been discontinued from study treatment and should have conducted the remaining visits according to the alternative schedule.

Abbreviations: ABA=abatacept; ADA=adalimumab; AZA=azathioprine; COX-2-cyclooxygenase 2; CTX=cyclophosphamide; CYC=cyclosporine; ETN=etanercept; GOL=golimumab; HCQ=hydroxychloroquine; IFX=infliximab; ia=intra-articular; IL=interleukin; im=intramuscular; iv=intravenous; LEF=leflunomide; MMF=mycophenolic acid; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; RTX=rituximab; SSZ = sulfasalazine; TCZ=tocilizumab; TNF=tumor necrosis factor; TOF=tofacitinib; UST=ustekinumab
[Source: UCB. AS0006 Interim CSR, Table 3-2. Dated Sep 4, 2018: pages 44-45]

Dose selection

UCB notes that, in study AS001, both CZP 200mg Q2W and CZP 400mg Q4W were found to be efficacious, and, as already described in Section 3, CZP is approved at these doses for the treatment of patients with AS in the US and Canada. In the EU, it is also approved for nr-axSpA at these doses. Thus, based on this knowledge, UCB chose to further evaluate the 200mg Q2W dose in study AS0006.

Study Treatments

Patients received the following study treatments:

- CZP 400mg at initiation, Weeks 2 and 4, and then 200mg Q2W for maintenance
- PBO at the same dosing intervals

CZP was supplied as a sterile, clear, colorless to slightly yellow liquid solution (pH 4.7) in a 1 mL single-use glass prefilled syringe (PFS) with a 25G ½ inch thin wall needle for SC injection. Each syringe contained an extractable volume of 1mL at a concentration of 200mg/mL of CZP in (b) (4) sodium acetate buffer an (b) (4) sodium chloride as (b) (4) PBO was supplied in a PFS with a 25G ½ inch thin wall needle, containing an injectable volume of 1mL 0.9% saline for single use. UCB reports that there was a difference in presentation and viscosity between CZP and PBO. Thus, special precautions were taken in order to ensure blinding of the study.

Assignment to Treatment

An interactive voice response system (IXRS) was used for patient registration as well as randomization and treatment administration. To enroll a patient, the Investigator contacted the IXRS and provided brief details of the patient to be enrolled. Each patient was then assigned a unique patient number.

Randomization was stratified by geographical region (North America, Europe, Asia) and MRI/CRP classification centrally evaluated (MRI+/CRP+, MRI+/CRP-, MRI-/CRP+).[9] The IXRS was designed to ensure that at least 20% of the randomized patients belonged to each of the 3 clinical subgroups. To randomize a patient, the Investigator contacted the IXRS and provided brief details of the patient; the IXRS automatically informed the Investigator of the patient's randomization number. Each patient was assigned a unique randomization number, which was required for all communications between the Investigator and the IXRS. The IXRS allocated kit numbers to the patients based on the randomization number. Patients were allocated to treatment in a 1:1 ratio (CZP 200mg:PBO).

Blinding

All patient treatment details were allocated and maintained by the IXRS. The study was designed as double-blind and placebo-controlled for 52 weeks. No study team member involved in the clinical conduct had access to the randomization schedule until after database lock and unblinding. If the Investigator decided to discontinue the double-blind study treatment and initiate OL treatment, efforts were made to ensure that the blinding of the previously assigned double-blind study treatment was maintained. Therefore, if patients were transitioned to OL treatment with CZP, study personnel administered the 3 loading doses without disclosing to the patient the use of the PFS. After the last loading dose, the patient could have self-administered CZP. Similarly, for the SFE period, in order to maintain the blind for patients completing the Double-Blind Period, unblinded study staff administered study treatment (either loading dose if previously on PBO or CZP 200mg/PBO if previously on CZP) at the study site on Weeks 52, 54, and 56.

Trial Location

One hundred four centers screened patients, and 80 centers enrolled patients. These centers were located in 9 countries, described in the Table of Clinical Trials (Section 7.1).

Administrative structure

The following key personnel were involved in this study.

- Principal/coordinating Investigator: Atul Deodhar, MD
- Monitoring contract search organization (CRO) (b) (4)
- Clinical Project Manager (b) (6)
- Clinical Therapeutic Area Physician (b) (6)
- Clinical Trial Biostatistician (b) (6)
- Imaging (b) (4)
- Interactive Voice Response System (IXRS (b) (4)

[9] The classification of MRI status for randomization, based on the ASAS/OMERACT definition, was at the Screening visit. The classification of CRP status was based on the second screening visit three to five days prior to randomization.

- Clinical trial supply management: UCB Pharma SA, Braine, Belgium
- Central laboratory facitlies for clinical laboratory assessments, neutralizing anti-drug antibody (nADA) assay, PK, anti-drug antibody (ADA)

Procedures and schedule

See the Appendix, Section 15.3, for the schedule of study assessments. These tables show the schedule for patients who stayed on double-blind treatment through Week 52 as well as the schedule for patients who discontinued double-blind treatment and switched to open-label CZP or other study treatments (including biologics).

MRI assessments were scheduled to be performed at baseline, Week 12, and Week 52. MRIs were read at Week 12 and at Week 52. At the first reading campaign, MRI readings were only included in analyses if patients had both baseline and Week 12 images. Similarly, at the second reading campaign, analysis and scoring were only performed if patients had a baselineand Week 52/WD image. Thus, not every patient was included in the first or second reading campaigns.

Treatment compliance

Drug accountability was recorded on the drug accountability form. If a patient was persistently noncompliant (missing ≥3 doses over the 52 week period), the patient was withdrawn from the study. No missing doses were allowed in the first 12 weeks of the study. If doses of the investigational medical product (IMP) were missed due to a reasonable AE that did not allow administration of an anti-TNF due to safety reasons, then these missed doses were not considered for evaluation of patient compliance.

Subject Completion, Discontinuation, or Withdrawal

Patients were free to withdraw from the study at any time without prejudice.

Patients were withdrawn from the study if the following occurred:

- Patients developed an illness that interfered with his/her continued participation.
- Patient was noncompliant with the study procedures or medications in the opinion of the Investigator.
- Patient withdrew his/her consent.
- There was confirmation of pregnancy during the study.
- UCB or a regulatory agency requested withdrawal of the patient.
- Patient's subsequent TB test was confirmed positive or any other evidence suggestive of potential TB infection (e.g., exposure).

Patients were withdrawn from study treatment if the following occurred:

- The Investigator decided to initiate an alternative treatment due to an unsatisfactory response to the study treatment.
- Patients took any of the prohibited medications.

For any patients who withdrew from double-blind study treatment, Investigators should have encouraged the patient to continue participation in the study in accordance with the appropriate alternative schedule (described under the Basic Study Design and Appendix Section 15.3). For patients who failed to return for any study visit or were considered lost to follow up, the Investigator should have specifically communicated (at least 1 phone call and 1 written message) with the patient. In cases when attempts to contact the patient failed, the Investigator was encouraged to gather information about the patient's wellbeing at the end of the regular visit schedule (e.g., Week 52).

Patients withdrawn from the study were not replaced. Please see the review of the Statistical Analysis Plan (SAP) below for a description of how patients who discontinued from the study were handled in statistical analyses.

Study Endpoints

The primary endpoint was the proportion of patients with ankylosing spondylitis disease activity score major improvement (ASDAS-MI) at Week 52 (Table 11). ASDAS[10] was a weighted score of signs and symptoms comprised from back pain based on question 2 of Bath ankylosing spondylitis disease activity index (BASDAI[11]), duration of morning stiffness based on question 6 of BASDAI, peripheral pain or swelling based on question 3 of BASDAI, patient's global assessment of disease activity, and CRP. A patient was a ASDAS-MI responder if the patient's change from baseline in ASDAS is ≥2.0 point reduction or had the lowest possible ASDAS post-baseline score (i.e., when CRP < lower limit of quantification, specified as 4 mg/L, and all other components are 0, giving an ASDAS score of 0.636).

[10] ASDAS was calculated as 0.121 x back pain + 0.058 x duration of morning stiffness + 0.073 x peripheral pain/swelling + 0.110 x patient global + 0.579 x log(CRP (mg/L) + 1). All components were assessed on a numerical rating scale (NRS) from 0 to 10 units except for CRP.
[11] BASDAI was a self-reported instrument that consists of six 10-unit horizontal NRS to evaluate severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness.

Table 11. Components of ASDAS and ASAS Endpoints

	ASDAS	ASAS
Patient Global Assessment	√	√
CRP	√	
Total Spinal Pain		√
BASFI		√
BASDAI components		
Qn 1 (Fatigue)		
Qn 2 (neck, back, hip pain)	√	
Qn 3 (pain/swelling in joints)	√	
Qn 4 (discomfort)		
Qn 5 (morning stiffness) [a]		√
Qn 6 (duration of morning stiffness) [a]	√	√
BASMI		

a: The Applicant described the average of question 5 and 6 of BASDAI as "inflammation concerning morning sickness."
Abbreviations: ASDAS=Ankylosing Spondylitis Disease Activity Score; ASAS=Assessment of SpondyloArthritis international Society; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; BASDAI= Bath ankylosing spondylitis disease activity index; CRP=C-reactive protein
[Source: Statistical Reviewer]

To preserve the overall type I error of 0.05, the step-down testing approach was used to evaluate the list of ordered endpoints when the primary efficacy endpoint result was statistically significant. The list was as follows: (1) ASAS40[12] response at Week 12; (2) the change from baseline in BASDAI at Week 12; (3) the change from baseline in Bath ankylosing spondylitis functional index (BASFI[13]) at Week 12; (4) ASAS40 at Week 52; (5) the change from baseline in BASDAI at Week 12; (6) the change from baseline in BASFI at Week 52; (7) the change from baseline in SI joint spondyloarthritis research consortium of Canada (SPARCC[14]) score at Week 12; (8) the change from baseline in ankylosing spondylitis quality of life

[12] ASAS response is made up of the domains detailed in Table 3. ASAS40 is defined as a relative improvement of at least 40% and absolute improvement of at least 2 units on a 0 to 10 NRS in at least 3 of the 4 domains and no worsening at all in the remaining domain.
[13] BASFI was a patient-reported outcome with a set of ten questions designed to determine the degree of functional limitation in patients with AS. A 0-10 numerical rating scale was be used to answer the questions, with 0 being "easy" and 10 being "impossible." The score would be derived from the mean of the ten items by the sponsor and was indicative of the patient's level of ability.
[14] The SPARCC scoring system is based on abnormal increased signal on the STIR sequence representing bone marrow edema. The total SPARCC Score (TSS) range from 0 to 72.

(ASQoL[15]) at Week 52; (9) the change from baseline in nocturnal spinal pain[16] based on numerical rating scale (NRS) at Week 52; (10) and the number of patients with anterior uveitis (AU) or new AU flares through Week 52.

Statistical Analysis Plan

Descriptive statistics were reported by the Applicant. Continuous variables were summarized and reported using the minimum, 25th percentile, mean, median, 75th percentile, maximum, and standard deviation. Binary or categorical variables were summarized and reported as counts and percentages. All datasets used for the statistical analysis were based on all randomized patients who received at least a dose of study treatment or the modified intent-to-treat (mITT) dataset.

The statistical reviewer described the Applicant's estimand using the four components: (1) the population targeted by the scientific question, (2) the variable or endpoint to be contained for each patient which is necessary to address the scientific question, (3) specification of handling intercurrent events, and (4) the choice of population-level summary for the variable which defines the comparison between treatment conditions[17].

To address the primary objective of the study, the Applicant specified that they were interested in targeting the composite estimand where a patient was considered an ASDAS-MI responder if they achieved an ASDAS-MI response at Week 52; and remaining on randomized double-blinded study treatment through Week 52. Patients who discontinued randomized treatment prior to Week 52, or did not have an ASDAS-MI response at Week 52, or were missing efficacy assessments due to lost to follow-up or withdrawal of informed consent were imputed as non-responders. The population to be targeted was all randomized patients, defined through the inclusion/exclusion criteria. The endpoint was ASDAS-MI response at Week 52, where a response was meeting the change from baseline criteria of at least 2 points reduction in ASDAS from baseline or having the lowest possible ASDAS post-baseline score , and remaining in the study and on randomized treatment at Week 52. The intercurrent event (discontinuation of randomized treatment prior to Week 52) was captured through the variable definition. Finally, the population-level summary is the difference in log odds of ASDAS-MI response comparing CZP and placebo. This estimand was used to evaluate the key secondary endpoints ASAS40 at Week 12 and Week 52.

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[15] ASQoL is an 18-item questionnaire developed to measure health-related quality of life in patients with AS. Each item has a "yes" or "no" answer, with "yes" contributing 1 to the total score. The scores for the questionnaire range from 0 (good quality of life) to 18 (poor quality of life).

[16] Pain was measured by 2 separate questions to address total pain in the spine due to axSpA and pain in the spine at night due to axSpA. A 10% difference (i.e., 1-point difference on NRS ranging from 0 to 10) is considered the MCID.

[17] ICH E9 (R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm582738.pdf

The ASDAS-MI responder endpoint at Week 52 was fit using a logistic regression adjusting for treatment group, region, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) ascertained from the source data. Specifically, the CRP assessment at the second screening visit (3-5 days prior to randomization) was used to derive the MRI/CRP classification. The SAP indicated that if the logistic regression model was unable to converge, then the MRI/CRP variable may be dropped from the model to facilitate convergence. Adjusted odds ratios (OR), 95% Wald-based confidence intervals (CI), and Wald-based p-values was reported. This regression model was applied for ASAS40 at Week 52 and ASAS40 at Week 12.

Because the proposed estimand relied on adherence to randomized study treatment through Week 52, a supportive analysis that isolated adherence to randomized treatment to directly assess the effect of CZP, relative to placebo, on the signs and symptoms at Week 52 is critical. The Applicant specified four supportive analysis. They included (1) an analysis based on all observed data collected at Week 52; (2) multiple imputation; (3) tipping point analysis; (4) an observed case analysis.

The first analysis would be reasonable to directly evaluate the effect on the signs and symptoms. The target estimand was the difference in log-odds of ASDAS-MI response at Week 52 comparing CZP and placebo in all randomized patients regardless of treatment adherence or use of ancillary therapies (open label or not). To target this estimand, patients who discontinue randomized treatment early would ideally be followed for all regularly safety and efficacy assessments and remain to provide inform consent to continue study participation. In this study, patients who discontinued randomized treatment were to return for a Week 52 efficacy assessment.

For the primary estimand, non-responder imputation was used to impute patients with missing data as non-responders . Because non-responder imputation was one form of single imputation procedure that directly imputed outcomes for patients with missing data as a failure, such an analysis would not appropriately address the uncertainty of the imputation process. To alleviate these concerns, the sponsor specified the multiple imputation (MI) analysis to account for this uncertainty. Specifically, the Applicant stated that the assumption of their procedure was that “missing efficacy data due to study treatment discontinuation should depend on the observed efficacy scores but independent of unobserved data.” The MI procedure was applied on the continuous ASDAS score derived from each visit. Last observation carried forward (LOCF) was used if one component was missing. Data collected after patients initiated OL CZP were excluded from the MI procedure. The method of Markov Chain Monte Carlo (MCMC) imputed missing intermittent ASDAS scores using treatment, region (categorical), and MRI/CRP classification (categorical) as covariates and created 100 different monotone datasets. For each monotone dataset, the remaining missing ASDAS score up to Week 52 was sequentially imputed using a regression model, based only on randomized treatment data and the imputed data, including treatment, region, MRI/CRP classification, and all ASDAS measurements from all previous visit. The imputed ASDAS outcome was dichotomized to create ASDAS-MI. The logistic regression model used for the primary analysis was applied on each of the 100 imputed datasets and Rubin’s rule (implemented using PROC

MIANALYZE) was used to combine the estimates of log-odds in ASDAS-MI response from the 100 imputed datasets to create the MI point estimates, respective 95% CIs, and p-values. This procedure was applied to the components of ASAS, prior to deriving the ASAS40 or ASAS20 responder endpoint. Unlike single imputation approaches, the MI approach accounted for the uncertainty using multiple imputation. However, this procedure only evaluated a specific potentially plausible assumption for missing data.

To reliably address other potential plausible assumptions, the Applicant included a tipping point analysis to address the impact of missing data on the robustness of their study's primary results. The imputed data from the MI procedure previously described was used as a starting point for the tipping point analysis. To generate the tipping point space, the delta shifts, with values ranging from 0 to 1.8, were applied independently on the CZP and placebo arm to the ASDAS-MI scores for each of the imputed dataset to cover the tipping point space.

The Applicant conducted an "observed case analysis" by including observed data for patients still on the randomized study treatment. Data collected after the discontinuation of study treatment and all other missing data were excluded from the logistic regression analysis. The statistical reviewer noted that this analysis was an on-treatment analysis and the Agency had previously communicated to the Applicant to revise the naming of this statistical analysis (electronic correspondence dated May 24, 2018).

For continuous endpoints, the Applicant was interested in targeting a hypothetical estimand under the setting where use of CZP or other biologics was not available to patients prior to Week 52. The population was all randomized patients. The variable was the continuous efficacy endpoint at week of interest. The intercurrent event would be the scenario where the use of OL CZP or other biologics was not available to any patients prior to Week 52, or did not discontinue randomized treatment. The estimand was the difference in means comparing CZP relative to placebo in the change from baseline in the continuous endpoint at the week of interest under the hypothetical scenario where the use of biologic medications was not available as medications prior to Week 52 and that their disease course would be like those from the placebo treated group. A linear regression was fit to the change from baseline adjusting for baseline measurement, treatment, region, and MRI/CRP classification, assuming homoscedasticity between groups of patients. Point estimates comparing difference in adjusted means between CZP and placebo, respective 95% CI, and p-values were reported. In other words, patients' data collected after use of OL CZP was ignored.

To handle missing data and patients who discontinued randomized treatment, a reference based multiple imputation procedure was used to impute missing efficacy assessments and patients who initiated OL CZP. The reference-based multiple imputation assumed that drug- and placebo-treated patients with missing values and the drug- and placebo treated patients who initiated OL CZP behave statistically like those placebo-treated patients. In this approach, multiple imputation replaced missing outcomes for drug- and placebo-treated patients who had missing data or discontinued treatment, using multiple draws from the regression model including treatment, region, MRI/CRP classification, and all continuous measurements from all

previous visit estimated from the placebo patients. Rubin's rule was then used to combine the multiple imputation results.

The Applicant specified further a supportive analysis based on all observed data collected at Week 52. The population was all randomized patients. The variable was a continuous efficacy endpoint at the Week 52 or Week 12. There was no intercurrent event. The target estimand was the difference in means comparing CZP relative to placebo in the change from baseline in the continuous endpoint at the week of interest regardless of adherence to randomized treatment or use of biologic medications. Missing data would be naturally excluded from the linear regression.

To further address the impact of missing data on this statistical analysis, the Applicant then included multiple imputation to impute patients who did not have data collected at week of analysis. The procedure replaced the missing outcomes for drug- and treated patients estimated from a regression model adjusting for treatment group and covariates of interest. Rubin's rule was applied to combine the point estimates obtained from fitting the linear regression model to the imputed datasets.

In addition, the Applicant conducted a completer's analysis based on patients who completed study and remained on randomized treatment. As noted previously, the target estimand was not clearly specified in the SAP and would not be reviewed.

The continuous patient reported outcome Short-Form 36-Item Health Survey (SF-36) was included in this review. In particular, the Applicant conducted statistical analysis for SF-36 physical component score (PCS), SF-36 mental component score (MCS), and the individual components of SF-36. The data collected from patients who discontinued randomized treatment were considered missing in the statistical analysis. Instead, for these patients, last observation carried forward (LOCF) was used to impute the data for timepoints from week of discontinuation through Week 52. A linear regression model was then fit to the change from baseline continuous outcome adjusting for baseline value, treatment group, categories of geographic region, and MRI/CRP classification. Estimated adjusted differences in means comparing CZP and placebo, respective 95% CI, p-values were reported.

For each subgroup analysis, the Applicant fit a logistic regression to the ASDAS-MI response based on the composite estimand. The model was further adjusted for the subgroup and interaction of the subgroup with treatment variable. Point estimates based on ORs for each subgroup, respective 95% Wald-based CI from the full regression model were reported.

Additional Reviewer Analyses

The primary endpoint ASDAS-MI at Week 52 is a multi-component endpoint that differentially weighed the direct measures of how patients feel and function in daily life (as measured by the patient reported outcomes (BASDAI questions)) and acute phase reactants such as CRP. Hence, significant results based on ASDAS-MI response should be supported by trends of improvements with magnitudes that are considered clinically relevant in the components of ASDAS-MI. Therefore, the statistical reviewer conducted analyses on the individual

components of ASDAS-MI to evaluate the effect of CZP relative to placebo on treatment of signs and symptoms of nr-axSpA based on all efficacy assessments collected regardless of adherence to randomized treatment, use of other biologics (CZP or other treatments). The statistical reviewer noted that the Applicant had conducted analysis for some of these components to target the treatment policy estimand using all observed data collected after initiation of OL CZP.

The key secondary endpoints ASAS40 at Week 12 and Week 52 were considered important from a regulatory perspective. Therefore, the statistical reviewer included supportive analyses for these individual components of ASAS40 to isolate the effect of adherence to evaluate the impact of CZP on signs and symptoms of the disease.

The statistical reviewer included ASDAS-MI trends using the primary composite estimand with NRI for patients with missing data or had switched to OL CZP or other treatments. The statistical reviewer included supportive analysis of the trends of ASDAS-MI response across the visit weeks of AS0006 based on all observed data collected regardless of adherence to randomized treatment, or use of OL CZP and conservatively use non-responder imputation (NRI) for patients who were (1) lost-to-follow-up; (2) withdrawal of informed consent to participate in the study; (3) discontinuation of randomized treatment.

During the review process, the statistical reviewer identified several limitations to the interpretation of the analysis results addressing the treatment policy estimand, i.e., the difference in treatment effect among all randomized patients on CZP relative to placebo regardless of adherence to randomized treatment, or use of biologics. Because the study protocol allowed patients to cross-over to OL CZP or other biologics, the knowledge of the use of OL CZP by patients and investigators when patients cross-over can impact subjective assessment of important clinical outcomes. This can influence the study results such that the observed differences (such as ASQoL, SF-36, patient global) between arms can be affected due to differences in patient expectations, or clinician expectations of what works, rather than differences in drug effects. Differential rates of initiation of OL CZP between arms further affected the reliability of the data collected after Week 12 to directly target the treatment policy estimand.

Efficacy assessments after initiating OL CZP, following discontinuation of randomized treatment, were limited. The schedule of assessments depends on when OL CZP was initiated. Hence, missing data were induced by design for patients who switched to OL CZP. Although patients who switched to OL CZP were to return for a Week 52 assessment since randomization, there were missing assessments between Weeks 12 and 52, especially after Week 20.

Therefore, given the limitations of the efficacy data collected from patients who switched to OL CZP, differential rates of initiation of OL CZP after Week 12, the potential bias of efficacy assessments for continuous endpoints due to knowledge of treatment using CZP, the statistical reviewer conducted analysis of the primary endpoint ASDAS-MI, and its components using all observed data collected regardless of adherence or use of ancillary medications at earlier time

points when discontinuation to OL CZP is limited. Similarly, individual components of ASAS40, BASMI, BASDAI, and BASFI were evaluated at earlier time points for similar reasons.

To facilitate evaluation of benefit:risk, the statistical reviewer included point estimates for continuous endpoints and respective 95% CIs to facilitate review. For responder endpoints, point estimates of difference in proportions, with 95% CIs using normal approximation, were included.

The Applicant had conducted tipping point analyses for the primary endpoint, proportion of ASDAS-MI responder, to evaluate the robustness of their primary efficacy results to missing data assumptions. The Applicant excluded any observed data collected after patients had discontinued randomized treatment in the tipping point analysis. However, patients who either discontinued randomized treatment and transitioned to OL CZP (or other treatments), or were lost to follow up, or withdrawal of informed consent to contribute efficacy assessments in the study were imputed to be like patients remaining on randomized treatment.

To target the treatment policy estimand, the statistical reviewer conducted tipping point analyses using all observed efficacy data collected to evaluate the effect of CZP relative to placebo. Systematic shifts were used to impute placebo patients who were truly missing the primary endpoint of interest at the week of visit to have better outcomes than placebo patients with observed data. Likewise, systematic shifts for patients on the CZP arm without the endpoint of interest at week of visit were allowed to vary independently over a range of worse outcomes than CZP patients with observed data. The tipping point method utilized was based on a large sample approximation of the distribution of the test statistic and is limited since it does not adjust for baseline covariates or intermediate outcomes. However, the approach provided a convenient approach to evaluate the missing data space.

(b) (4)

However, the Applicant used LOCF for patients who discontinued randomized treatment or discontinued randomized treatment and initiated OL CZP, or were lost-to-follow-up, or had withdrawn consent to participate in the study. Because the knowledge of assignment to CZP can affect patient's expectation of a treatment effect or lack thereof, the statistical reviewer also conducted supportive analysis at earlier time points to assess the effect of CZP relative to placebo in patient reported outcomes when the impact of switching to OL CZP were minimal.

Subgroup analysis for demographics and key clinical characteristics was evaluated using stratified logistic regression adjusting for treatment group. Due to potential small number of patients in specific stratification categories, the statistical reviewer conducted subgroup analysis adjusting only for treatment group in the logistic regression. When possible, i.e., there are responses by treatment group in each subgroup category, a Bayesian shrinkage hierarchical model was used to evaluate and describe potential heterogeneity of treatment effects across subgroups.

Protocol Amendments

Study AS0006 was originally submitted on June 1, 2015. It had a total of four global protocol amendments and seven local protocol amendments. The four global amendments are described in the table below.

Table 12. Global Amendments, Study AS0006

Global Amendments	Date	Major Modifications
Amendment 1	December 15, 2015	• The procedures and assessments were clarified. Some supporting information were added, and errors/inconsistencies were removed. • A range of sensitivity analyses to evaluate the impact of missing data on the primary efficacy variable was added. • The exclusion criterion regarding the upper limit of normal (ULN) of the liver function tests for patients who were not taking MTX was changed. • The requirement for plasma samples to be analyzed to confirm the washout of specific prohibited medication was removed. • The reporting needs of physician completed assessments in the eCRFs were clarified. • Two tables were included to assist Investigators in identifying the assessments to be performed when patients switched to alternative treatments. For example, for patients who discontinued the study treatment during Study Period 2, the assessments completed at the scheduled visit did not need to be repeat at the withdrawal treatment Week 0 visit of the alternative schedule. • Inconsistencies in the laboratory assessments performed, the definition of study treatment, and the use of Week 52 and Week 52/WD Visit were corrected. • MRI for the spine was to be performed at Week 12, along with the already planned SI MRI. • "Are Patient-Report Outcome Instruments for Ankylosing Spondylitis Fit-For-Purpose for the Axial Spondyloarthritis Patient? A Qualitative and Psychometric Analysis" by van Tubergen, et al. was published, and the protocol was updated to reflect the publication.
Amendment 2	March 14, 2016	• Study procedures were clarified. • Inclusion Criteria 5 and 6 concerning ASAS criteria were updated. ○ For Inclusion Criterion 5, it was clarified that ASAS criteria were classification criteria, not diagnostic criteria, to avoid misinterpretation.

		○ For Inclusion Criterion 5, the part regarding "at least 12 months of symptom duration before Screening" was removed. Instead, it was added to Inclusion Criterion 6, which was about patients having evidence of inflammatory back pain as defined by ASAS criteria. • The number of participating sites and screened patients were increased from 95 to 120 and from 900 to 1200, respectively, to adjust for a higher screening failure rate, which exceeded the expected rate of 67%. • Text about chest x-ray at Screening was updated to clarify that chest x-rays were done at Screening unless a chest x-ray (or CT chest) was done within 3 months prior to the Screening visit. • Text about study treatment administration at on-site visits was clarified to detail at which visits the SC injections were administered by dedicated, unblinded, and adequately trained site personnel or by self-injection of the patients under the supervision of the unblinded study personnel.
Amendment 3	February 13, 2017	• Clarifications were made regarding the additional 2 years of OL CZP treatment that was provided to eligible patients after completion of the Week 52 visit. This OLE was named the SFE Period, and the protocol was updated to include an additional Schedule of Study Assessments, eligibility criteria, study treatment administration, and concomitant medications for this period. • Female patients who became pregnant during AS0006 were given the option to enroll in a separate, observational, pregnancy follow-up study. • The 40% cap on IXRS randomization to each of the 3 clinical subgroups for MRI/CRP (i.e., MRI+/CRP+, MRI+/CRP-, or MRI-/CRP+) was removed to reflect the real world. • Clarification that cases of potential Hy's Law were ALWAYS to be reported to UCB as an AE of interest, i.e., without waiting for any additional etiologic investigations to be concluded.
Amendment 4	December 19, 2017	• An alternative primary efficacy variable of ASAS40 at Week 12 was implemented for Canada and any other country where applicable or where requested by Regulatory Authorities. Thus, for these same countries, ASDAS-MI at Week 52 was moved to the list of secondary efficacy variables. • For all countries, the following 3 efficacy variables were

		added to the bottom of the testing hierarchy list. ○ Change from Baseline in AS-QoL at Week 52 (elevated from “other” to “secondary” efficacy variable) ○ Change from Baseline in nocturnal spinal pain NRS at Week 52 (elevated from "other" to "secondary" efficacy variable) ○ Number of patients with anterior uveitis (AU) or new AU flares through Week 52 (new efficacy variable) • The assay for measuring anti-CZP/anti-drug antibody (ADA) in plasma samples was replaced with new methods in order to align with current regulatory guidelines. This replacement was made across the entire CZP development program. • The Medical Outcomes Study (MOS) Sleep Scale was updated to reflect the newer 5-point scale.

[Source: Clinical Reviewer]

These modifications were reasonable, and are unlikely to impact the integrity of the trial or interpretation of the results.

8.1.2. AS0006: Study Results

Data Quality and Integrity

Data were submitted by the Applicant to the CDER electronic data room in SAS transport format. Protocols, correspondence, data listings, program code, and study reports were accessed under the network path \\CDSESUB1\evsprod\BLA125160\. During the review process, several information requests were made to facilitate review of this application (Table 13).

A comprehensive documentation, including an Imaging Charter, was provided for this review and was considered adequate.

The statistical reviewer reviewed the quality and integrity of the submitted data and sent several IRs to the Applicant. (Table 13). The statistical reviewer noted that the legacy tabulation datasets and legacy analysis datasets were inconsistent. Subsequent information requests (IRs) were sent to request for clarifications. The Applicant resubmitted the correct tabulation data on November 05, 2018. The legacy tabulation datasets were compared with the legacy analysis datasets and were consistent for review of this application.

Table 13. Data Links, Dates, and Summary of Information Requests

Information request links	Date of response	Summary
0563	October 16, 2018	Protocol versions, SAP, analysis datasets for study AS0006, programs and macros, and safety signal detection charter
0564	October 30, 2018	Randomization list, including CRP value at screening and randomization
0565	November 01, 2018	Randomization list sequence
0566	November 05, 2018	CRF for all patients
0567	November 05, 2018	Discrepancies between tabulation and analysis datasets
0569	December 04, 2018	Radiograph screening values
0571	December 13, 2018	Justification of 400 mg Q4W dosing
0574	January 11, 2019	Disposition table, subgroup analysis, radiograph endpoint
0577	January 31, 2019	Follow-up on disposition table submitted in 0574
0579	January 31, 2019	Efficacy of 400 mg in Study AS001

Abbreviations: DMC=Data Monitoring Committee; IWRS=interactive web response system; IVRS=interactive voice response system; IWRS=interactive web response system; SAP=statistical analysis plan; Q4W=every four weeks; CRP=C-reactive protein; CRF=clinical research forms
[Source: Statistical Reviewer]

In the submitted clinical study report, the Applicant noted that the source data used for randomization were different from the randomization data for magnetic resonance imaging (MRI) and/or elevated C-reactive protein (CRP). In the response to the IR dated October 30, 2018, the Applicant provided a summary of the number of patients where their randomization data submitted through Interactive Voice/Web Response System (IXRS) were inconsistent with the source data (Table 14). The Applicant noted that the misclassification between IXRS and source data occurred "when the information on MRI and CRP entered by the investigator after the first screening visit (MRI/CRP classification per the IXRS) is updated using the MRI/CRP classification from the source data obtained from centralized MRI reading and central lab results for CRP after the second screening." The Applicant noted that three of the patients with incorrect MRI/CRP classification were randomized into the study. Two of which were discovered early during the study; the third patient was only discovered during unblinding after the first database lock and included in all the intent-to-treat dataset but excluded from the per-protocol analysis (Table 15). The statistical reviewer noted according to the protocol, the CRP classification used for randomization was based on the second screening visit. Further, there were minimal discrepancies between IXRS and source data based on the review. Further, the Applicant had documented procedures on how to capture these discrepancies and prespecified how to handle them in the statistical analysis plan (SAP).

Table 14. Concordance Table Comparing MRI/CRP Classification using IXRS Data vs Source Data vs Classification used for Statistical Analysis

IXRS classification	Source data classification	Analysis classification	CZP 200 mg SC Q2W	PBO
MRI-/CRP+	MRI-/CRP-	MRI-/CRP+	1	0
MRI-/CRP+	MRI-/CRP+	MRI-/CRP+	37	37
MRI-/CRP+	MRI+/CRP-	MRI+/CRP-	1	0
MRI-/CRP+	MRI+/CRP+	MRI+/CRP+	1	0
MRI+/CRP-	MRI-/CRP-	MRI-/CRP+	1	1
MRI+/CRP-	MRI+/CRP-	MRI+/CRP-	70	73
MRI+/CRP-	MRI+/CRP+	MRI+/CRP+	1	0
MRI+/CRP+	MRI-/CRP+	MRI-/CRP+	1	2
MRI+/CRP+	MRI+/CRP-	MRI+/CRP-	3	3
MRI+/CRP+	MRI+/CRP+	MRI+/CRP+	43	42

Discrepancies between IXRS and Source data are highlighted in red.
Abbreviation: CZP=Certolizumab Pegol; MRI=magnetic resonance imaging; CRP=C-reactive protein; Q2W=once every two weeks; IXRS=Interactive Voice/Web Response System; SC=subcutaneously
[Source: Statistical Reviewer]

Table 15. Listings of Patients who had IXRS Classification Different from Source Data

Subject ID	Arm	Site ID	Region	CRP	CRP Group 1	CRP Group 2	IXRS	Source
(b) (6)	CZP	(b) (6)	NA	45	>ULN	>LLOQ	MRI+/CRP+	MRI-/CRP+
	PBO		Europe	2	≤ULN	≤LLOQ	MRI+/CRP-	MRI-/CRP-
	CZP		Europe	2	≤ULN	≤LLOQ	MRI+/CRP-	MRI-/CRP-
	CZP		Europe	2	≤ULN	≤LLOQ	MRI+/CRP+	MRI+/CRP-
	CZP		Europe	8.27	≤ULN	>LLOQ	MRI+/CRP+	MRI+/CRP-
	CZP		Europe	13.8	>ULN	>LLOQ	MRI+/CRP-	MRI+/CRP+
	PBO		Europe	9.52	≤ULN	>LLOQ	MRI+/CRP+	MRI+/CRP-
	CZP		Europe	2	≤ULN	≤LLOQ	MRI-/CRP+	MRI-/CRP-
	CZP		Europe	11.45	>ULN	>LLOQ	MRI-/CRP+	MRI+/CRP+
	PBO		Europe	9.91	≤ULN	>LLOQ	MRI+/CRP+	MRI+/CRP-
	PBO		Europe	39.41	>ULN	>LLOQ	MRI+/CRP+	MRI-/CRP+
	PBO		Europe	36.72	>ULN	>LLOQ	MRI+/CRP+	MRI-/CRP+
	CZP		Europe	2	≤ULN	≤LLOQ	MRI-/CRP+	MRI+/CRP-
	PBO		Europe	8.05	≤ULN	>LLOQ	MRI+/CRP+	MRI+/CRP-
	CZP		Europe	4.17	≤ULN	>LLOQ	MRI+/CRP+	MRI+/CRP-

Patients in red did not meet the inclusion/exclusion criteria. Patient (b) (6) was discovered only after Week 52 while the other two patients in red were discovered early on and withdrawn from the study.
Abbreviations: CRP=C-reactive protein; MRI=magnetic resonance imaging; ULN=upper limit of normal; LLOQ=lower limit of quantification; NA=North America
[Source: Statistical Reviewer]

In summary, the data and source documentation requested were considered adequate for review of this application.

Compliance with Good Clinical Practices

Study AS0006 was conducted in accordance with the current version of the applicable regulatory and International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved. In addition, patient's informed consent was obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Financial Disclosure

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators, per 21 CFR 54 and the *Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators*. The Applicant provided a list of all clinical investigators. Of the 519 investigators, one received a significant payment with a cumulative value of $25,000 or more; this payment was described a (b) (6) (b) (4). The Applicant has also provided the measures it took to mitigate the possibility of bias for investigators that have reported significant contributions from UCB on the financial disclosure form. These steps include assessment of primary/secondary variables under a double-blind treatment design, continuous on-site monitoring for adherence to the study protocol, collection and assessment of protocol deviations, and oversight of safety reporting of AEs by the Medical Monitor. Additionally, for the investigator who received the significant payment in this study, the Applicant noted that this investigator screene (b) (6) out of 954 patient (b) (6) Thus, in regard to the financial disclosures for study AS0006, there are no issues that should affect approvability of this application.

Patient Disposition

A total of 317 screened patients with active non-radiographic axial spondyloarthritis (nr-axSpA),[18] with X-ray evaluated centrally to ascertain they were not mNY+ (up to six weeks prior to randomization), were randomized in a 1:1 ratio to CZP 200 mg SC Q2W (n=159) or placebo (n=158), in combination with standard of care.

[18] Patients with objective signs of inflammation at baseline (defined by elevated CRP values and/or sacroiliiitis on MRI), back pain for at least 12 months before screening, and not have sacroiliiitis defined by modified New York criteria on sacroiliac joint x-rays were included in the study.

Of the 317 patients randomized, 90% of the patients completed Week 52 study visit (Table 16). However, only 57.4% of the patients remained on randomized treatment, with disproportionately more CZP patients remaining on randomized treatment.

At Week 12, 99% of the patients completed the study visit (i.e., the patient had a Week 12 visit regardless of whether they had discontinued randomized study treatment or not). No randomized patients had switched to OL other treatments, except one CZP patient who switched to OL CZP later switched to OL other treatments. A total of seven patients had discontinued the study or did not have assessments for Week 12 visit. Overall, more placebo patients discontinued the study for reasons of adverse events (Table 17).

Table 16. Patient Disposition at Weeks 12 and 52

	PBO (N=158)	CZP 200 mg SC Q2W (N=159)	ALL (N=317)
Completed Week 12 visit	155 (98%) [1]	155 (97%) [1]	310 (98%)
On randomized treatment	155 (98%)	155 (97%)	310 (98%)
Discontinued study[2]/Lost to follow-up	3 (1%) [2]	4 (1%) [3]	4 (1%)
Completed Week 52 visit	143 (91%)	142 (89%)	285 (90%)
On randomized treatment	54 (34%)	125 (79%)	137 (57%)
On OL CZP	89 (56%)	17 (11%)	106 (33%)
Discontinued study[2]/Lost to follow-up	15 (10%) [3]	17 (11%) [4]	32 (10%)

Counts and percentages are presented with respect to the number of patients randomized.
1: One placebo patient and two CZP patient did not have Week 12 efficacy assessments and regarded to not complete Week 12 visit.
2: Patients who discontinued randomized treatment and withdraw informed consent, or had withdrawn informed consent, or were lost-to-follow up were recorded in this row.
3: Two patients on placebo arm and one patient from CZP had their last dose of randomized treatment at day 238, 262, and day 295 respectively. Week 52 data were not collected from these patients. The discontinuation reasons for the two placebo patients were adverse event and non-compliant (Others).
4: The CZP patient had the last randomized treatment at day 295. The discontinuation reason was noted to be lack of efficacy. The last ASDAS collection day was 309. The patient withdrew consent on day 365. The statistical reviewer disagreed with the Applicant's classification that they were still on originally randomized treatment.
Summary statistics for the other rows are counts and percentages relative to N.
Abbreviations: CZP=certolizumab pegol; SC=subcutaneously; PBO=placebo; OL=open label
[Source: Statistical Reviewer]

Table 17. Reasons for Discontinuation of Study Prior to Week 52

	PBO (N=158)	CZP 200 mg SC Q2W (N=159)	ALL (N=317)
Discontinued study/Lost to follow-up	15 (10%)	17 (11%)	32 (10%)
Adverse event	6	3	9
Lack of efficacy	2	2	4
Protocol deviation	1	1	2
Withdrawal by patient	3	7	10
Lost-to follow-up	2[1]	-	2
Other	1[2]	4[3]	5

1: One patient without a disposition date was lost-to-follow up. The statistical reviewer noted that the patient had a study exit date beyond Week 52.
2: The reason reported was non-compliant.
3: The reasons for the four patients were: non-compliant, patient's decision; "as per suggestion"; and patient is not eligible for the study.
Abbreviations: CZP=certolizumab pegol; SC=subcutaneously; PBO=placebo
[Source: Statistical Reviewer]

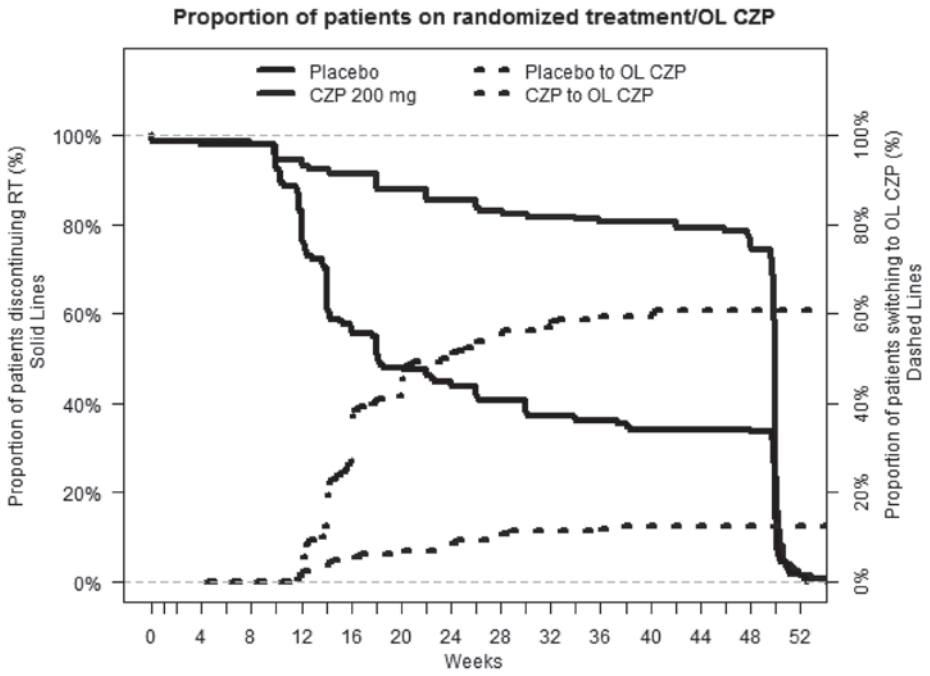
A total of 138 patients discontinued randomized treatment (Table 18) prior to Week 52. A total of 116 patients had started OL CZP prior to Week 52, and a markedly high proportion of placebo patients started OL CZP. A majority of the patients switched to OL CZP between Week 12 and Week 20 (Figure 7., Table 62).

Table 18. Reasons for Discontinuation of Randomized Treatment Prior to Week 52

	PBO (N=158)	CZP 200 mg SC Q2W (N=159)	ALL (N=317)
Discontinued randomized treatment	104 (66%)	34 (21%)	138 (44%)
Lack of efficacy	91[1]	20	107
Protocol deviation	2[1]	2	4
Other	11[1]	12[3]	23
Started OL CZP	96 (61%)	20 (13%)	116 (37%)

1: Four were noted to have lack of efficacy for discontinuation. Two was noted to be non-compliant with study procedures and thus interpreted to be protocol deviation. Remaining 11 patients had adverse events, withdrawal of informed consent, pregnancy as Others for reason.
2: The remaining twelve patients reported AEs, withdrawal of informed consent, or worsening of treatment symptoms.
Abbreviations: CZP=certolizumab pegol; SC=subcutaneously; PBO=placebo; OL=open label; Q2W=every two weeks
[Source: Statistical Reviewer]

Figure 7. Proportion of Patients on Randomized Treatment Over Time or Switched to OL CZP



Dotted lines represent the cumulative proportion of patients who discontinued randomized treatment and started OL CZP.
Abbreviations: CZP=certolizumab pegol; PBO=placebo; OL=open label; RT=randomized treatment
[Source: Statistical Reviewer]

Protocol Violations/Deviations

Protocol deviations were those which could have potentially had a meaningful impact on study conduct or on the primary efficacy outcome for an individual patient. The Applicant had verified that important protocol deviations were reviewed as part of the ongoing data cleaning process, and important deviations were identified and documented prior to unblinding to confirm exclusion from analysis sets.

Most of the patients (68.5%) had no important protocol deviations. Fifty-six patients (35.2%) in the CZP arm and 44 patients (27.8%) in the PBO arm experienced at least 1 important protocol deviation. The most frequently reported important protocol deviation was procedural non-compliance (32 patients [20.1%] in the CZP arm and 25 patients [15.8%] in the PBO arm). UCB determined that the important protocol deviations did not invalidate the safety and efficacy objectives of the study.

Patient Characteristics

Baseline demographics were comparable for both arms (Table 19). Patients randomized into the study were mostly white. Only 9% of the patients were from North America. Anthropometric variables were comparable across arms.

Table 19. Baseline Demographics for Randomized Patients

	Placebo (N=158)	CZP 200 mg SC Q2W (N=159)	All (N=317)
Age (years) [1]	37.4 (10.8) 18 - 67	37.3 (10.5) 18 - 73	37.3 (10.6) 18 - 73
Age ≥ 45 years	39 (25%)	34 (21%)	73 (23%)
Male	76 (48%)	78 (49%)	154 (49%)
Race			
White	148 (94%)	152 (96%)	300 (95%)
Black	1 (1%)	0 (0%)	1 (0%)
Asian	8 (5%)	5 (3%)	13 (4%)
Other	1 (1%)	2 (1%)	3 (1%)
Ethnicity			
Hispanic or Latino	1 (1%)	3 (2%)	4 (1%)
Not (Hispanic or Latino)	157 (99%)	156 (98%)	313 (99%)
Geographic Region			
North America	13 (8%)	15 (9%)	28 (9%)
Europe	130 (82%)	130 (82%)	260 (82%)
Asia	15 (9%)	14 (9%)	29 (9%)
Weight (kg) [1]	79 (18.0) 42 - 136	78 (16.6) 45 - 126	79 (17) 42 - 136
Height (cm) [1]	172 (9.8) 147 - 194	171 (10.2) 149 - 196	171 (10.0) 147 - 196
BMI (kg/m^2) [1]	27 (6.1) 17 - 47	27 (5.3) 18 - 45	27 (5.7) 17 - 47

1: Mean and standard deviation in parenthesis are presented on the first row; Minimum to maximum are presented on the second row.
Summary statistics for the other rows are counts and percentages relative to N.
Abbreviations: CZP=certolizumab pegol; SC=subcutaneously; Q2W=every two weeks; BMI=body mass index
[Source: Statistical Reviewer]

Other Baseline Characteristics

Baseline disease characteristics were largely similar on average across arms (Table 20). The mean time since diagnosis was 3.8 years, and the mean duration of symptoms was 7.9 years. Most of the patients (82%) were positive for HLA-B27, and 52% of the patients had CRP above upper limit of normal. Based on the inclusion criteria, all patients had to have an objective measure of inflammation, categorized as MRI+/CRP+, MRI-/CRP+, and MRI+/CRP-. The study protocol specified that all classifications of inflammation to be represented by >20% of the patient population. The proportions of classifications of objective inflammation were similar

across treatment arms. A greater proportion of patients (46%) were MRI+/CRP-, whereas 24% of patients were MRI-/CRP+ and 30% MRI+/CRP+.

Table 20. Baseline Disease Characteristics for Randomized Patients

	Placebo (N=158)	CZP 200 mg SC Q2W (N=159)	All (N=317)
Baseline CRP (mg/L) [1]	15.8 (17.7) 2 - 99	15.8 (17.8) 2 - 110	15.8 (17.7) 2 - 110
CRP≤ULN	77 (49%)	75 (47%)	152 (48%)
CRP>ULN	81 (51%)	84 (53%)	165 (52%)
CRP≤LLOQ	53 (34%)	51 (32%)	104 (33%)
CRP>LLOQ	105 (66%)	108 (68%)	213 (67%)
MRI/CRP classification			
MRI-/CRP+	37 (23%)	40 (25%)	77 (24%)
MRI+/CRP-	74 (47%)	72 (45%)	146 (46%)
MRI+/CRP+	47 (30%)	47 (30%)	94 (30%)
Duration of disease (years) [1]	4.0 (5.4) 0 - 38	3.6 (4.8) 0 - 29	3.8 (5.1) 0 - 38
≥5 years	38 (24%)	34 (21%)	72 (23%)
Duration of primary symptom (years) [1]	8.0 (7.5) 1 - 38	7.8 (7.7) 1 - 42	7.91 (7.6) 1 - 42
≥5 years	81 (51%)	79 (50%)	160 (50%)
Presence of enthesitis at baseline	122 (77%)	125 (79%)	247 (78%)
Positive HLA-B27 Genotype	133 (84%)	128 (81%)	261 (82%)
Baseline SPARCC score	7.8 (10.8) 0 – 43.5	8.5 (12.3) 0 - 56	8.1 (11.6) 0 - 56
<5	89 (56%)	89 (56%)	178 (56%)
≥5	64 (41%)	66 (42%)	130 (41%)
Missing	5 (3%)	4 (3%)	9 (3%)
Baseline X-ray [1]	0.65(0.54) 0 - 2	0.67(0.53) 0 - 2	0.66 (0.53) 0 - 2
Missing	5 (3%)	4 (3%)	9 (3%)

1: First row=Mean (standard deviation); Second row=minimum – maximum
Summary statistics for the other rows are counts and percentages relative to N.
Abbreviations: CZP=certolizumab pegol; SC=subcutaneously; BMI=body mass index; CRP=C-reactive protein; ULN=upper limit of normal; LLOQ=lower limit of quantification; MRI=magnetic resonance imaging; HLA-B27=human leukocyte antigen B27; SPARCC=Spondyloarthritis Research Consortium of Canada
[Source: Statistical Reviewer]

The baseline efficacy measures were generally similar across treatment arms (Table 21).

Table 21. Baseline Characteristics for the Key Efficacy Endpoints for all Randomized Patients

Efficacy measures	Placebo (N=158)	CZP 200 mg SC Q2W (N=159)	All (N=317)
ASDAS[1]	3.8 (0.8)	3.8 (0.8)	3.8 (0.8)
PGADA[2]	6.7 (2.0)	6.8 (1.9)	6.8 (2.0)
BASDAI[2]	6.8 (1.3)	6.9 (1.4)	6.8 (1.3)
Q1: Overall level of fatigue	7.2 (1.4)	7.1 (1.6)	7.2 (1.5)
Q2: Overall spondylitis neck back or hip	7.4 (1.3)	7.4 (1.4)	7.4 (1.4)
Q3: Pain/swelling in joints	6.2 (2.2)	6.3 (2.3)	6.2 (2.2)
Q4: Discomfort areas tender to touch	6.4 (1.9)	6.7 (1.9)	6.5 (1.9)
Q5: Level of morning stiffness	7.2 (1.8)	7.3 (1.7)	7.3 (1.7)
Q6: How long morning stiffness last	6.2 (2.4)	6.5 (2.3)	6.3 (2.4)
Inflammation: *Average of Q5 and Q6*	6.7 (1.8)	6.9 (1.8)	6.8 (1.8)
BASFI [2]	5.4 (2.2)	5.4 (2.1)	5.4 (2.1)
Q1: Putting on socks or tights	4.1 (2.5)	4.2 (2.6)	4.1 (2.5)
Q2: Bending forward from waist to floor	5.3 (2.7)	5.3 (2.5)	5.3 (2.6)
Q3: Reaching up to a high shelf	4.8 (2.7)	4.7 (2.5)	4.7 (2.6)
Q4: Getting up out of armless chair	5.1 (2.7)	5.2 (2.6)	5.1 (2.7)
Q5: Getting up off the floor	6.2 (2.7)	6.3 (2.7)	6.2 (2.7)
Q6: Standing unsupported 10 minutes	5.6 (2.7)	5.8 (2.6)	5.7 (2.6)
Q7: Climbing 12 - 15 steps w/o aid	4.9 (2.9)	5.0 (2.8)	4.9 (2.8)
Q8: Looking over shoulder w/o turning body	5.3 (2.8)	5.3 (2.6)	5.3 (2.7)
Q9: Doing physically demanding activities	6.5 (2.3)	6.3 (2.4)	6.4 (2.3)
Q10: Doing a full day's activities	6.6 (2.2)	6.2 (2.1)	6.4 (2.2)
BASMI[2]	2.8 (1.4)	3.0 (1.3)	2.9 (1.3)
CRP (mg/L)	15.8 (17.7)	15.9 (17.8)	15.9 (17.7)
Total spinal pain[2]	6.9 (1.8)	7.0 (1.9)	7.0 (1.8)
Nocturnal spinal pain[2]	6.6 (2.1)	6.6 (2.3)	6.6 (2.2)

Means and standard deviation in parenthesis are presented above
1: ASDAS is computed as 0.121 * BASBAI Q2 + 0.058 BASDAI Q6 + 0.110 * PGADA + 0.073 * BASDAI Q3 + 0.579 * (natural logarithm of (CRP + 1)). Note that CRP values below the prespecified lower limit of quantification of (<4mg/L) will be imputed as 2 mg/L for computation purposes.
2: The components of the endpoints are evaluated numerical rating scale (NRS) from 0 to 10. The BASFI score is averaged over the 10 components.
Abbreviations: ASDAS=Ankylosing Spondylitis Disease Activity Score; PGADA=Patient's Global Assessment of Disease Activity; NRS=numerical rating scale; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; SC=subcutaneously; Q2W=every two weeks; CZP=certolizumab pegol; w/o=without
[Source: Statistical reviewer]

The baseline patient reported outcomes for AS-QoL and SF-36 PCS and MCS were balanced across treatment groups (Table 22).

Table 22. Baseline Patient Reported Outcomes for Randomized Patients

PROs	Placebo (N=158)	CZP 200 mg SC Q2W (N=159)	All (N=317)
AS-QoL[1]	12.1 (4.3)	11.7 (4.3)	11.9 (4.3)
SF-36 PCS[2]	33.7 (7.0)	34.6 (7.1)	34.2 (7.0)
Bodily pain	33.9 (6.3)	33.2 (6.2)	33.6 (6.2)
General Health	36.3 (7.5)	38.3 (7.5)	37.3 (7.6)
Physical Functioning	35.4 (9.2)	36.5 (9.0)	35.9 (9.1)
Role Physical	34.6 (7.4)	35.3 (7.9)	35.0 (7.7)
SF-36 MCS	41.2 (10.1)	42.0 (11.0)	41.6 (10.5)
Mental Health	39.6 (10.0)	39.3 (10.4)	39.4 (10.2)
Role Emotional	40.5 (10.8)	41.7 (11.0)	41.1 (10.9)
Social Functioning	36.7 (9.7)	37.8 (10.1)	37.3 (9.9)
Vitality	36.8 (8.2)	38.7 (8.2)	37.8 (8.3)

Abbreviations: PROs=patient reported outcomes; AS-QoL=Ankylosing Spondylitis Quality of Life; PBO=placebo; CZP=certolizumab pegol; SF-36=Short-Form 36-Item Health Survey; BP=bodily pain; GH=general health; PF=physical functioning; RP=role physical; MH=mental health; RE=role emotional; SF=social functioning; VT=vitality; MCS=mental component score; PCS=physical component score
[Source: Statistical Reviewer]

Table 23 presents the patients' history of medication use pertinent for the treatment of nr-axSpA (e.g., NSAIDs) at baseline. Most patients were previously treated with NSAIDs; in fact, 56.2% of patients were previously treated with ≥3 NSAIDs. Most patients (52.7%) had not been previously treated with a DMARD or a TNF-antagonist.

Table 23. Concomitant Medications at Baseline

	PBO N=158 n (%)	CZP 200mg Q2W N=159 n (%)	All Patients N=317 n (%)
Prior use of NSAIDs			
0	4 (2.5)	2 (1.3)	6 (1.9)
1	10 (6.3)	14 (8.8)	24 (7.6)
2	47 (29.7)	62 (39.0)	109 (34.4)
≥ 3	97 (61.4)	81 (50.9)	178 (56.2)
Prior use of DMARDs			
0	85 (53.8)	82 (51.6)	167 (52.7)
1	39 (24.7)	46 (28.9)	85 (26.8)
2	20 (12.7)	14 (8.8)	34 (10.7)
≥ 3	14 (8.9)	17 (10.7)	31 (9.8)
Allowed concomitant DMARDs at Baseline			
0	110 (69.6)	106 (66.7)	216 (68.1)
1	43 (27.2)	49 (30.8)	92 (29.0)
2	5 (3.2)	4 (2.5)	9 (2.8)
≥ 3	0	0	0
Prior TNF-antagonist exposure			
No	147 (93.0)	152 (95.6)	299 (94.3)
Yes	11 (7.0)	7 (4.4)	18 (5.7)

Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; NSAIDs=non-steroidal anti-inflammatory drugs; DMARDs=disease modifying anti-rheumatic drugs; TNF=tumor necrosis factor
[Source: UCB, AS0006 Interim Clinical Study Report, Table 7-7. Dated Sep 24, 2018: page 159-60.]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Most patients on both treatment arms were compliant with the protocol. Based on the number of syringes per patient, the mean compliance ratio was 0.993 for both the PBO and CZP arms. Fourteen patients (8.9%) in the PBO arm and 10 patients (6.3%) in the CZP arm had <80% compliance based on the day of administration.

Patients were permitted to take concomitant medications for nr-axSpA and to adjust these medications as described in Table 10. Most patients (68.1%) did not take a concomitant DMARD (Table 23). On the other hand, most patients (87.1%) did take a concomitant NSAID.

At the discretion of the Investigator, some patients were switched to other treatments, namely OL CZP, to achieve better disease control, preferably after Week 12. See the above section regarding Patient Disposition for a review of the proportion of patients who transitioned to other treatments at various time points through the study.

Efficacy Results – Primary Endpoint

At Week 52, 47% of the patients randomized to CZP and 7% of the patients randomized to placebo achieved an ASDAS-MI response and remained in the study on randomized treatment (Table 24). There was statistically significantly higher probability of ASDAS-MI response comparing CZP with placebo. Adjusting for geographic region and categorical classification of MRI/CRP, the estimated odds ratio (OR) of ASDAS-MI response and remaining in the study on randomized treatment at Week 52 comparing all randomized CZP patients relative to all randomized placebo patients was 15.2 (95% CI: 7.3, 31.6; p<0.001).

Table 24. ASDAS-MI Response at Week 52 Based on Composite Estimand

	Placebo (N=158) Count (%)	CZP 200 mg SC Q2W (N=159) Count (%)	Estimated OR[1] (95% CI; p-value)	Estimated Diff[2] (95% CI)
Responders	11 (7%)	75 (47%)	15.2 (7.3, 31.6; p<0.001)	40% (7.0%, 47.2%)

Non-responder imputation was used for patients who discontinued randomized treatment and went on open-label CZP or other treatments, or were lost-to-follow-up, missing components of ASDAS, or did not have a Week 52 visit.
1: Odds ratio and 95% Wald-based confidence intervals based on a logistic regression fit to ASDAS-MI response adjusting for treatment, geographical region, and MRI/CRP classification.
2: Difference in proportions with 95% CI based on normal approximation.
Abbreviations: CZP=certolizumab pegol; OR=odds ratio; SC=subcutaneously; ASDAS-MI=Ankylosing Spondylitis Disease Activity Score Major Improvement; NRI=non-responder imputation; CI=confidence interval; MRI=magnetic resonance imaging; CRP=C-reactive protein
[Source: Statistical Reviewer]

As a supportive analysis, based on all observed data analysis including efficacy assessments collected after patients were switched to OL CZP were used, the probability of ASDAS-MI response at Week 52 regardless of adherence to randomized treatment assignment, or use of open label study remained significantly in favor of the CZP arm relative to placebo patients (Table 25), with an estimated adjusted OR of 2.2 (95% CI: 1.3, 3.6). The estimated lower CI of 1.3 was larger than 1, the null hypothesis of no effect in OR. However, the interpretation of the results using a treatment policy estimand was difficult and likely biased because these results could be driven by the differential use of OL CZP use across arms, patients' knowledge of treatment, expectations of treatment benefit, and investigator's expectations of effectiveness, rather than differences in drug effects.

Table 25. ASDAS-MI Response at Week 52 Based on all Observed Data

	Placebo (N=158) Count (%)	CZP 200 mg SC Q2W (N=159) Count (%)	Estimated OR[1] (95% CI; p-value)	Estimated Diff[2] (95% CI)
Responders	52 (33%)	78 (49%)	2.2 (1.3, 3.6; p=0.002)	16% (4.8%, 27.5%)
Non-responders	82 (52%)	60 (38%)		
Missing imputed as non-responder[3]	24 (15%)	21 (13%)		

1: Odds ratio and 95% Wald-based CI based on a logistic regression fit to ASDAS-MI response adjusting for treatment, geographical region, and MRI/CRP classification.
2: Difference in proportions with 95% CI based on normal approximation
3: Non-responder imputation was used for patients who were lost-to-follow-up, missing components of ASDAS, or did not have a Week 52 visit
Abbreviations: CZP=certolizumab pegol; OR=odds ratio; SC=subcutaneously; NRI=non-responder imputation; CI=confidence interval; ASDAS-MI=Ankylosing Spondylitis Disease Activity Score Major Improvement;
[Source: Statistical Reviewer]

Numerically consistent trends of benefit towards CZP relative to placebo were observed at scheduled visit weeks based on the probability of ASDAS-MI responders and remained on randomized treatment and in the study among all randomized patients (Table 26). As a supportive analysis, using all observed data collected regardless of discontinuation of randomized treatment, there were numerically consistent trends of benefit, though weaker, towards CZP relative to placebo based on the probability of ASDAS-MI responders regardless of discontinuation of randomized treatment. The magnitude of the efficacy results based on all observed data collected is difficult to interpret and is further impacted by disproportionate missing efficacy assessments between Weeks 24 and 52.

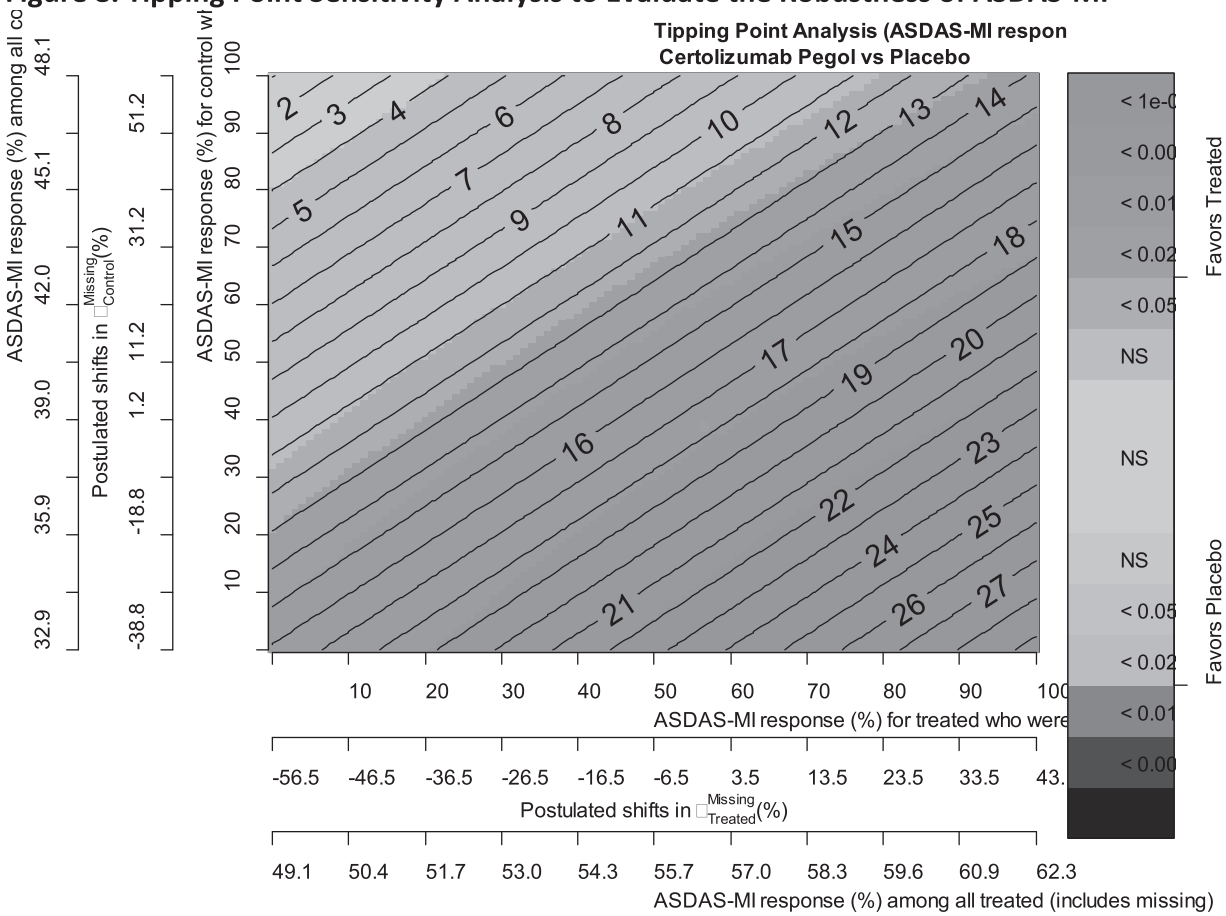
Table 26. ASDAS-MI Response at each Visit for the Composite Estimand and all Observed Data Collected

Week	*Composite Estimand*[1]			*All observed data collected regardless of discontinuation of randomized treatment*[2]				
	PBO (N=158) Count (%)	CZP 200 mg SC Q2W (N=159) Count (%)	Est Diff % (95% CI)[3]	PBO (N=158) NAs	Count (%)	CZP 200 mg SC Q2W (N=159) NAs	Count (%)	Est Diff % (95% CI)[3]
2	2 (1.3%)	33 (20.8%)	19% (12.3% - 26.7%)	1	2 (1.3%)	3	33 (20.8%)	19% (12.3% - 26.7%)
4	5 (3.2%)	38 (23.9%)	21% (12.9% - 28.5%)	2	5 (3.2%)	3	38 (23.9%)	21% (12.9% - 28.5%)
8	6 (3.8%)	48 (30.2%)	26% (18.0% - 34.8%)	3	6 (3.8%)	3	48 (30.2%)	26% (18.0% - 34.8%)
12	10 (6.3%)	56 (35.2%)	29% (19.9% - 37.9%)	3	10 (6.3%)	4	56 (35.2%)	29% (19.9% - 37.9%)
16	13 (8.2%)	58 (36.5%)	28% (19.0% - 37.5%)	6	15 (9.5%)	4	58 (36.5%)	27% (17.6% - 36.4%)
20	11 (7.0%)	63 (39.6%)	33% (23.5% - 41.9%)	25	20 (12.7%)	11	63 (39.6%)	27% (17.1% - 36.8%)
24	13 (8.2%)	61 (38.4%)	30% (20.8% - 39.5%)	48	23 (14.6%)	15	61 (38.4%)	24% (13.8% - 33.8%)
28	13 (8.2%)	65 (40.9%)	33% (23.3% - 42.0%)	42	31 (19.6%)	13	66 (41.5%)	22% (11.4% - 32.4%)
32	15 (9.5%)	71 (44.7%)	35% (25.6% - 44.8%)	74	24 (15.2%)	25	71 (44.7%)	29% (19.3% - 39.6%)
36	11 (7.0%)	69 (43.4%)	36% (27.1% - 45.7%)	70	22 (13.9%)	22	70 (44.0%)	30% (20.1% - 40.1%)
40	11 (7.0%)	72 (45.3%)	38% (29.0% - 47.6%)	55	32 (20.3%)	25	73 (45.9%)	26% (15.1% - 36.3%)
44	12 (7.6%)	69 (43.4%)	36% (26.4% - 45.2%)	86	22 (13.9%)	30	70 (44.0%)	30% (20.1% - 40.1%)
48	13 (8.2%)	68 (42.8%)	35% (25.1% - 44.0%)	94	15 (9.5%)	31	69 (43.4%)	34% (24.3% - 43.5%)
52	11 (7.0%)	75 (47.2%)	40% (30.9% - 49.6%)	24	52 (32.9%)	21	78 (49.1%)	16% (4.8% - 27.5%)

Counts and percentages (relative to N) are presented. Missing data (see 1 and 2) were conservatively imputed as failures.
1: NRI was used to impute ASDAS-MI outcome for patients who had discontinued randomized treatment and initiated OL CZP, or were missing ASDAS data at week of analysis, or were lost-to-follow-up.
2: NRI was used to impute ASDAS-MI outcome for patients who were missing ASDAS data at week of analysis or were lost-to-follow-up.
3: Difference in proportions and 95% CI based on normal approximation to difference in proportions
Abbreviations: CZP=certolizumab pegol; OR=odds ratio; SC=subcutaneously; ASDAS-MI=Ankylosing Spondylitis Disease Activity Score Major Improvement; PBO=placebo; Q2W=every two weeks; NRI=non-responder imputation; NAs=number of patients with missing ASDAS-MI data; CI=confidence interval
[Source: Statistical Reviewer]

The proportion of patients without any Week 52 observed components of ASDAS-MI data was 15% and 13% for placebo and CZP arm respectively. Tipping point analyses that varied the assumptions about the ASDAS-MI response rate in these patients without Week 52 data are shown in CZP comparison with placebo (Figure 8.). Missing placebo patients at Week 52 from would have to have at least 60% response rates, together with a responder rates of 30% from CZP arm to tip the conclusions, such that there would no longer be evidence of an effect. However, most patients discontinued for lack of efficacy reasons and therefore the described scenario is unlikely to be reasonable. Additional tipping point analyses were conducted for ASDAS-MI responder at Week 12. These results were robust to departures of missing data assumption.

Figure 8. Tipping Point Sensitivity Analysis to Evaluate the Robustness of ASDAS-MI



Abbreviations: ASDAS-MI=Ankylosing Spondylitis Disease Activity Score Major Improvement; NS=not significant (p-value > 0.05)
[Source: Statistical Reviewer]

At Week 12, there were statistically significant improvements in ASDAS and all components of based on all individual data collected regardless of discontinuation of randomized treatment (Table 27). Estimated effects for the individual components at Week 52 showed numerical trends of benefit towards CZP relative to placebo (Table 62). These observed trends could have been driven by the disproportionate number of patients who had initiated OL CZP by Week 52, knowledge of treatment potentially influencing patient's expectations and investigators' expectation of effectiveness.

Table 27. Analyses of the Individual Components of ASDAS-MI at Week 12 Based on all Observed Data

	PBO Mean (SD)	CZP 200 mg SC Q2W Mean (SD)	Placebo (N=158)	CZP 200 mg SC Q2W (N=159)	Estimated Diff (95% CI)
ASDAS	3.3 (1.0) (n=155)	2.3 (0.9) (n=155)	-0.5 (0.9) (n=155)	-1.6 (1.0) (n=155)	-1.1 (-1.3, -0.9)
Patient global	5.9 (2.4) (n=155)	3.8 (2.6) (n=155)	-0.8 (2.5) (n=155)	-3.0 (2.8) (n=155)	-2.1 (-2.7, -1.6)
BASDAI Q2: Back pain	6.2 (2.1) (n=155)	4.1 (2.5) (n=155)	-1.2 (2.1) (n=155)	-3.3 (2.3) (n=155)	-2.1 (-2.6, -1.6)
BASDAI Q3: Peripheral pain/swelling	5.3 (2.5) (n=155)	3.7 (2.4) (n=155)	-0.9 (2.6) (n=155)	-2.6 (2.8) (n=155)	-1.7 (-2.2, -1.2)
BASDAI Q6: Duration of morning stiffness	5.1 (2.7) (n=155)	3.3 (2.4) (n=155)	-1.1 (2.4) (n=155)	-3.2 (2.5) (n=155)	-1.9 (-2.4, -1.4)
CRP(mg/L)	13.2 (17.2) (n=155)	6.7 (15.1) (n=155)	-2.6 (14.9) (n=155)	-9.2 (19.5) (n=154)	-6.6 (-9.8, -3.5)

1: Mean and standard deviation in parenthesis are presented with number of observations at week of analysis
2: Linear regression adjusting for treatment and stratification factors
Abbreviations: CZP=certolizumab pegol; SC=subcutaneously; Q2W=every two weeks; CI=confidence interval; ASDAS=Ankylosing Spondylitis Disease Activity; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; CRP=C-reactive protein; SD=standard deviation; Diff=difference
[Source: Statistical Reviewer]

Efficacy Results – Secondary and other relevant endpoints

The observed probability of ASAS40 response and remaining on randomized treatment at Week 12 among all randomized patients on CZP was 48% while the observed probability of ASAS40 response and remaining on blinded randomized treatment at Week 12 among all randomized patients on placebo was 11% (Table 28). There was statistically significantly higher probability of ASAS40 response at Week 12 comparing CZP-treated patients with placebo-treated patients, with an estimated OR of 7.4 (95% CI, 4.1, 13.4) after adjusting for geographic region and categorical classification of MRI/CRP. Results at Week 52 for ASAS40 were also statistically significant.

Table 28. Proportion of ASAS Response on Randomized Treatment at Key Visit Weeks Based on the Primary Composite Estimand

	Placebo (N=158) Counts (%)	CZP 200 mg SC Q2W (N=159) Counts (%)	Estimated OR[1] (95% CI)	Estimated Diff[2] (95% CI)
ASAS40				
Week 12	18 (11.4%)	76 (47.8%)	7.4 (4.1, 13.4)	36.4% (26.6%, 46.2%)
Week 24	26 (16.5%)	81 (50.9%)	5.5 (3.3, 9.4)	34.5% (24.2%, 44.8%)
Week 36	29 (18.4%)	90 (56.6%)	6.0 (3.6, 10.0)	38.2% (27.8%, 48.7%)
Week 52	25 (15.8%)	90 (56.6%)	7.4 (4.3, 12.6)	40.8% (30.6%, 51.0%)

Non-responder imputation was used to impute patients on randomized treatment who did not have an efficacy assessment at week of analysis, or patients who discontinued randomized treatment, or patients who transitioned to OL CZP or other treatments, or were lost-to-follow-up, or had withdrawn from the study.
Counts and percentages (relative to N) in parenthesis were reported.
1: ORs and respective 95% Wald based CI were reported based on a logistic regression model adjusting for treatment, geographical region, and MRI/CRP classification. All p-values were <0.001
2: Reviewer's re-analysis of the endpoint based on a difference in proportions analysis and respective 95% CI using normal approximation to difference in proportions.
Abbreviations=ASAS; CZP=certolizumab pegol; SC=subcutaneously; Q2W=every two weeks; OR=odds ratios; CI=confidence interval
[Source: Statistical Reviewer]

Because no patients had initiated OL CZP at time of efficacy assessement at Week 12, the observed probability of ASAS40 response regardless of adherence to study drug at Week 12 among all randomized patients on CZP was similar to the sponsor's composite estimand results at Week 12 (Table 29). Interpretation of findings at Week 24 and 36 were impacted by differential rates of switching to OL CZP and limited efficacy assessments after switching to OL CZP. At Week 52, results based on all observed data collected regardless of adherence to study drug or switching to OL CZP remained statistically significant, with an estimated OR of 1.9 (95% CI: 1.2, 2.9) among all randomized patients comparing CZP with placebo. Results based on Week 52 should be cautiously interpreted due to potential differential rates of switching to OL CZP, knowledge of treatment, and patient expectation of benefit.

Table 29. Proportion of ASAS Response on Randomized Treatment at Key Visit Weeks Based on all Observed Data

	Placebo (N=158)		CZP 200 mg SC Q2W (N=158)		Est OR; (95% CI); p-value	Est Diff (95% CI)
	n	Counts (%)	n	Counts (%)		
ASAS40						
Week 12	155	18 (11.4%)	154	76 (47.8%)	7.4 (4.1, 13.4); <0.001	36.4% (26.6%, 46.2%)
Week 24	110	45 (28.5%)	144	81 (50.9%)	2.7 (1.7, 4.4); <0.001	22.5% (11.3%, 33.6%)
Week 36	88	47 (29.7%)	137	91 (57.2%)	3.3 (2.0, 5.3); <0.001	27.5% (16.4%, 38.6%)
Week 52	134	72 (45.6%)	138	95 (59.7%)	1.9 (1.2, 2.9); 0.01	14.2% (2.7%, 25.7%)

Non-responder imputation was used to impute patients who did not have an efficacy assessment at week of analysis, or were lost-to-follow-up, or had withdrawn from the study.
Counts and percentages (relative to N) in parenthesis were reported.
1: ORs and respective 95% Wald based CI were reported based on a logistic regression model adjusting for treatment, geographical region, and MRI/CRP classification. All p-values were <0.001
2: Based on a difference in proportions analysis and respective 95% CI using normal approximation to difference in proportions.
Abbreviations: ASAS=Assessment of Spondyloarthritis international Society; CZP=certolizumab pegol; Q2W=every two weeks; OR=odds ratios; SC=subcutaneously; CI=confidence interval; n=number of patients with efficacy data collected.
[Source: Statistical Reviewer]

At Week 12, there were significant improvements from baseline in the individual components of ASAS comparing CZP relative to placebo based on all observed data collected regardless of adherence to treatment or use of ancillary treatments (Table 30). At later time points, there was an observed numerical trend of benefit towards CZP relative to placebo. However, results at later time points after week 12 were impacted by differential use of OL CZP, and a different schedule of efficacy assessments such that results beyond week 12 were difficult to interpret.

Table 30. Mean Change from Baseline (SD) at Key Visit Weeks for Components of ASAS

Week	PBO Mean (SD) (N=158)	CZP Mean (SD) (N=159)	n	PBO Mean Change from Baseline (SD)	n	CZP Mean Change from Baseline (SD)	Diff (95% CI) [1]
Patient global							
Baseline	6.7 (2.0)	6.8 (1.9)					
12	5.9 (2.4)	3.8 (2.6)	155	-0.8 (2.5)	154	-3.0 (2.8)	-2.1 (-2.7, -1.6)
24	4.1 (2.5)	3.4 (2.6)	110	-2.5 (2.8)	143	-3.5 (2.7)	-0.8 (-1.4, -0.2)
36	3.6 (2.6)	3.0 (2.4)	88	-2.8 (2.7)	136	-3.9 (2.6)	-0.7 (-1.4, -0.1)
52	3.4 (2.5)	2.9 (2.4)	134	-3.3 (2.9)	138	-3.9 (2.7)	-0.5 (-1.0, 0.1)
Spinal pain							
Baseline	6.9 (1.8)	7.0 (1.9)					
12	6.0 (2.3)	3.9 (2.6)	155	-0.9 (1.9)	154	-3.1 (2.6)	-2.2 (-2.6, -1.7)
24	4.2 (2.6)	3.4 (2.5)	110	-2.5 (2.7)	143	-3.6 (2.5)	-0.9 (-1.5, -0.4)
36	3.5 (2.4)	3.0 (2.4)	88	-3.2 (2.5)	137	-4.1 (2.4)	-0.6 (-1.3, -0.0)
52	3.6 (2.5)	2.9 (2.4)	134	-3.3 (2.8)	138	-4.1 (2.5)	-0.7 (-1.3, -0.2)
BASFI							
Baseline	5.4 (2.2)	5.4 (2.1)					
12	4.9 (2.4)	3.2 (2.3)	155	-0.5 (1.8)	154	-2.2 (2.1)	-1.7 (-2.1, -1.3)
24	3.4 (2.4)	2.9 (2.4)	110	-1.8 (2.3)	143	-2.6 (2.2)	-0.6 (-1.1, -0.1)
36	3.0 (2.3)	2.6 (2.3)	88	-2.0 (2.2)	137	-2.8 (2.4)	-0.5 (-1.1, 0.0)
52	2.7 (2.3)	2.4 (2.3)	134	-2.6 (2.3)	138	-3.0 (2.3)	-0.3 (-0.8, 0.2)
Inflammation [1]							
Baseline	6.2 (2.4)	6.5 (2.3)					
12	5.1 (2.7)	3.3 (2.4)	155	-1.1 (2.4)	155	-3.2 (2.5)	-1.9 (-2.4, -1.4)
24	3.3 (2.4)	2.8 (2.4)	110	-2.5 (2.9)	144	-3.9 (2.5)	-0.8 (-1.4, -0.3)
36	2.7 (1.9)	2.6 (2.4)	88	-3.0 (2.6)	137	-4.0 (2.8)	-0.3 (-0.9, 0.2)
52	2.8 (2.4)	2.4 (2.3)	134	-3.4 (2.8)	138	-4.2 (2.7)	-0.5 (-1.0, 0.0)

1: Reviewer's analysis based on a linear regression adjusting for stratification factors, baseline covariate of interest, and treatment, assuming homoskedasticity between treatment groups.
Abbreviations: ASAS=Assessment of Spondyloarthritis international Society; SD=standard deviation; Q2W=every two weeks; CZP=certolizumab pegol; SC=subcutaneously; BASFI=Bath Ankylosing Spondylitis Functional Index; CI=confidence interval; n=number of patients with observed efficacy assessment
[Source: Statistical Reviewer]

At Week 12, the mean change from baseline in BASDAI was nominally statistically lower comparing CZP with placebo (Table 31). At later time points, the effect was attenuated, despite numerical trends of improvement towards CZP arm. These effects were also observed in BASMI (Table 32).

Table 31. Mean Change from Baseline at Key Visit Weeks for BASDAI based on all Observed Data Collected

Week	PBO Mean (SD) (N=158)	CZP Mean (SD) (N=159)	Placebo Mean Change from baseline (SD)	CZP Mean Change from baseline (SD)	Diff (95% CI)
Baseline	6.8 (1.3) (n=158)	6.9 (1.4) (n=159)			
12	5.7 (2.1) (n=155)	3.9 (2.2) (n=155)	-1.1 (1.9) (n=155)	-3.0 (2.1) (n=155)	-1.8 (-2.3, -1.4)
24	3.9 (2.2) (n=110)	3.4 (2.2) (n=144)	-2.7 (2.4) (n=110)	-3.5 (2.1) (n=144)	-0.7 (-1.2, -0.1)
36	3.5 (2.1) (n=88)	3.1 (2.2) (n=137)	-3.0 (2.3) (n=88)	-3.9 (2.2) (n=137)	-0.5 (-1.1, 0.1)
52	3.3 (2.1) (n=134)	2.9 (2.2) (n=138)	-3.5 (2.3) (n=134)	-4.0 (2.3) (n=138)	-0.4 (-0.9, 0.1)

1: Difference in means comparing CZP with PBO, respective 95% CI, based on Reviewer's analysis using a linear regression adjusting for stratification factors, baseline covariate of interest, and treatment, assuming homoskedasticity between treatment groups.
Abbreviations=ASAS; CZP=certolizumab pegol; SC=subcutaneously; Q2W=every two weeks; CI=confidence interval; n=number of patients with observed efficacy data
[Source: Statistical Reviewer]

At Week 12, the mean change from baseline in BASMI was nominally statistically lower comparing CZP with placebo (Table 32). At Week 52, there were numerical trends of improvement in BASMI comparing CZP with placebo, albeit the higher proportion of PBO patients on OL CZP.

Table 32. Mean Change from Baseline at Key Visit Weeks for BASMI based on all Observed Data Collected

Week	PBO Mean (SD) (N=158)	CZP Mean (SD) (N=159)	Placebo Mean Change from baseline (SD)	CZP Mean Change from baseline (SD)	Diff (95% CI)
Baseline	2.8 (1.4) (n=158)	3.0 (1.3) (n=159)			
12	2.7 (1.4) (n=151)	2.6 (1.4) (n=148)	-0.1 (0.9) (n=150)	-0.4 (0.9) (n=148)	-0.3 (-0.5, -0.1)
24	2.5 (1.3) (n=98)	2.4 (1.3) (n=138)	-0.1 (0.9) (n=98)	-0.5 (0.9) (n=138)	-0.3 (-0.5, -0.1)
36	2.4 (1.3) (n=85)	2.3 (1.2) (n=129)	-0.3 (1.1) (n=84)	-0.6 (1.0) (n=129)	-0.2 (-0.5, 0.0)
52	2.4 (1.1) (n=125)	2.3 (1.3) (n=132)	-0.4 (1.0) (n=124)	-0.6 (1.0) (n=131)	-0.2 (-0.4, 0.0)

1: Difference in means comparing CZP with PBO, respective 95% CI, based on Reviewer's analysis using a linear regression adjusting for stratification factors, baseline covariate of interest, and treatment, assuming homoskedasticity between treatment groups.
Abbreviations=ASAS; CZP=certolizumab pegol; SC=subcutaneously; Q2W=every two weeks; OR=odds ratios; CI=confidence interval; n=number of patients with observed data
[Source: Statistical Reviewer]

Imaging Endpoints

At Week 12, the mean SPARCC score for placebo patients was 8.5 while the mean SPARCC score for CZP patients was 2.8 (Table 33). As a sensitivity analysis, MRI assessed outside the visit windows was included as a re-analysis and did not affect the conclusions (Table 34).

Table 33. SI Joint SPARCC Score for Patients with a Post-baseline Assessment within Visit Window

	PBO (N=158) Mean (SD)	CZP 200 mg SC Q2W (N=159) Mean (SD)
Baseline MRI at week 12 based on all patients within visit window	8.2 (11.0) (n=140)	8.6 (12.5) (n=142)
MRI at week 12 based on all patients within visit window	8.5 (12.5) (n=142)	2.8 (5.4) (n=140)
Descriptive for visit windows	72 - 99	78 - 99

1: Note that differences in baseline MRI can be due to re-reads.
Abbreviations: SI=Sacroiliac; SPARCC=Spondyloarthritis Research Consortium of Canada; PBO=placebo; CZP=certolizumab pegol; SD=standard deviation; MRI=magnetic resonance imaging; SD=standard deviation; SC=subcutaneously; Q2W=every two weeks; n=number of patients with observed data

[Source: Statistical Reviewer]

Table 34. SI Joint SPARCC Score for Patients with any Post-baseline Assessment

	PBO (N=158) Mean (SD)	CZP 200 mg SC Q2W (N=159) Mean (SD)
MRI at week 12 base on all patients [1]	8.4 (12.3) (n=153)	2.7 (5.2) (n=154)
Descriptive for visit windows	72 - 140	67 - 128

1: Note that differences in baseline MRI can be due to re-reads.
Abbreviations: SI=Sacroiliac; SPARCC=Spondyloarthritis Research Consortium of Canada; PBO=placebo; CZP=certolizumab pegol; SD=standard deviation; MRI=magnetic resonance imaging; SD=standard deviation; SC=subcutaneously; Q2W=every two weeks; n=number of patients with observed data
[Source: Statistical Reviewer]

The clinical meaningfulness of this change in SPARCC score is unclear. The Applicant reported the proportion of patients who had a change in MRI status as defined using the criteria of an SI joint SPARCC score of the SI joints ≥ 2 to reflect MRI+ and <2 to reflect MRI-. This definition requires at least 2 BMO lesions to be present and is consistent with the ASAS/OMERACT definition of a positive assessment. The ASAS/OMERACT definition was used to determine MRI+ or MRI- at study entry. The proportion of patients who had an MRI status since baseline was reported in Table 35 and Table 36. At Week 12, more patients on CZP (30.0%) compared to patients on PBO (8.5%) were classified as MRI+ at Baseline and then MRI- at Week 12. Few patients overall but numerically more patients on PBO (9.2%) compared to patients on CZP (3.6%) were originally classified as MRI- at Baseline and then MRI+ at Week 12.

At Week 52, there were much fewer MRIs read in the PBO arm. However, based on analyses of those patients who had MRI readings at Baseline, Week 12, and Week 52, a similar finding was noted. A larger proportion of patients on CZP (38.4%) started as MRI+ at Baseline and then was MRI- at Week 52, compared to patients on PBO (24.3%). The proportion of patients on PBO may have been influenced by the number who switched to OL CZP. Few patients (7.1% on PBO and 3.2% on CZP) were re-classified from MRI- at Baseline to MRI+ at Week 52.

The role of MRI in disease monitoring is currently limited, and there is no clear correlation between clinical disease activity and inflammation on MRI.[19] It is notable, though, that more patients on CZP, who started with MRI findings of sacroiliitis by SPARCC criteria, were later noted to be MRI negative at Weeks 12 and 52.

[19] Lockwood M and Gensler L. *Best Pract Res Clin Rheumatol.* 2017; 31: 816-829.

Table 35. SI Joint SPARCC Status Changes between Baseline and Week 12

SI Joint SPARCC Status	PBO N=158	CZP 200mg Q2W N=159
n†	153	154
MRI+ (Baseline) → MRI- (Week 12)	13 (8.5%)	44 (28.6%)
MRI- (Baseline) → MRI+ (Week 12)	14 (9.2%)	7 (4.5%)

n† Number of patients with both Baseline and Week 12/early withdrawal assessments within a ± 2-week visit window
MRI+ = SI joint SPARCC Score ≥2; MRI- = SI joint SPARCC Score <2
Note: MRI Assessments at Week 12 come from the first efficacy reading campaign assessing Baseline and Week 12 only
Note: % are based on the number of patients with data (†)
Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; SI=sacroiliitis; SPARCC= Spondyloarthritis Research Consortium of Canada; MRI=magnetic resonance imaging
Source: UCB Response to Clinical IR, fda-q5-2019-02-01.pdf, Post hoc Table 4.5.8.1.2, dated 2/4/2019, page 3 of 57.

Table 36. SI Joint SPARCC Status Changes between Baseline and Week 52

SI Joint SPARCC Status	PBO		CZP 200mg Q2W	
	DB PBO N=62	All PBO N=158	DB CZP N=139	All CZP N=159
n†	53	70	121	125
MRI+ (Baseline) → MRI- (Week 52)	9 (17.0)	17 (24.3)	48 (39.7)	48 (38.4)
MRI- (Baseline) → MRI+ (Week 52)	5 (9.4)	5 (7.1)	4 (3.3)	4 (3.2)

n† Number of patients with both Baseline and Week 12 or Week 52/early withdrawal assessments within a ± 2-week visit window
MRI+ = Mean SPARCC Score ≥2; MRI- = Mean SPARCC Score <2
Note: MRI Assessments at Week 52 come from the second efficacy reading campaign assessing Baseline, Week 12, and Week 52
Note: % are based on the number of patients with data (†)
Note: Treatment groups DB PBO and DB CZP contain patients who remained on randomized treatment throughout the study. Patients who switched to OL CZP at any time throughout the study (even if they switched after their MRI) are not included in this table.
Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; SI=sacroiliitis; SPARCC= Spondyloarthritis Research Consortium of Canada; MRI=magnetic resonance imaging; DB=double blind
Source: UCB Response to Clinical IR, Table 4, dated 2/4/2019, page 8.

Radiographic assessment was evaluated at Week 52 for patients who remained on randomized treatment. The goal of the 52-week study was provide data on the natural history of progression in nr-axSpA patients. Part of the reason for this 52-week study was to cover a sufficiently long timeframe to potentially achieve an understanding of the natural history of nr-axSpA. Patients who switched to OL CZP were not required to have an x-ray assessment at Week 52. Therefore, only 69 placebo and 122 CZP patients remaining on randomized treatment had radiograph assessments within the pre-specified window (Table 65). Two PBO

patients and one CZP patient met mNY criteria, thus criteria for AS, at Week 52. It is difficult to make any assessment regarding predictors for progression given these low numbers. Even though the study was 52 weeks long, the study duration was not likely long enough to determine if, or at what rate, progression might occur in this study population.

Dose/Dose Response

Only one dose of CZP was investigated in Study AS0006, while an additional dosing regimen was studied in study AS001.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

At Week 12, adjusting for stratification factors and baseline ASQoL score, the estimated mean difference in the change from baseline in total ASQoL score based on all observed data was 3.5 points lower (95%CI: -4.4, -2.6; p<0.001) on CZP arm compared to placebo (Table 37). At Week 52, this estimated difference based on all observed patients regardless of discontinuation to OL CZP was -1.1 points lower (95% CI: -2.2, -0.000; p=0.0497) comparing CZP arm relative to placebo. Results based on Week 52 should be cautiously interpreted due to potential differential rates of switching to OL CZP, knowledge of treatment, and patient expectation of benefit. (b) (4)

(b) (4)

Table 37. AS-QoL at Various Weeks based on all Observed Data Collected

Week	PBO Mean (SD) (N=158)	CZP Mean (SD) (N=159)	PBO Mean Change from baseline (SD)	CZP Mean Change from baseline (SD)	Est Diff (95% CI) p-value
Baseline	12.1 (4.3) (n=158)	11.7 (4.3) (n=158)			
12	10.5 (5.2) (n=155)	6.7 (5.5) (n=155)	-1.6 (3.8) (n=155)	-5.0 (4.6) (n=155)	-3.5 (-4.4, -2.6) <0.001
52	5.9 (5.2) (n=133)	4.6 (5.0) (n=137)	-6.2 (5.4) (n=133)	-7.1 (5.0) (n=137)	-1.1 (-2.2, -0.0) 0.0497

1: Difference in means comparing CZP with PBO, respective 95% CI, based on Reviewer's analysis using a linear regression adjusting for stratification factors, baseline covariate of interest, and treatment, assuming homoskedasticity between treatment groups.
Abbreviations=ASAS; CZP=certolizumab pegol; SC=subcutaneously; Q2W=every two weeks; SD=standard deviation; CI=confidence interval; n=number of patients with observed efficacy data
[Source: Statistical Reviewer]

Clinical Reviewer's comments: The ASQoL is a PRO with questions that target pain, tiredness, daily activities, emotional impacts, and sleep; the scoring for ASQoL is described above in Section 8.1.1. Although ASQoL was on the predefined hierarchical testing sequence, it has not been previously used to support labeling for nr-axSpA. To support its use in endpoint labeling,

UCB submitted an evidence dossier which included a literature review, expert interviews, and qualititative patient interview to explore the relevance of the ASQoL items in patients with nr-axSpA. See separate review by the Clinical Outcome Assessment (COA) staff (Dr. Wen-Hung Chen) for details regarding the review of the acceptability of ASQoL for nr-axSpA. The COA staff agreed that the Applicant successfully demonstrated that ASQoL is a psychometrically reliable, valid, and treatment-responsive endpoint. COA's conclusion was that the ASQoL is fit-for-purpose for this development program to measure concepts relevant and important to patients with active nr-axSpA in the context of use. Thus, it is acceptable to include ASQoL in the labeling for nr-axSpA.

At Week 12, adjusting for stratification factors and baseline SF-36 score, there was nominally significantly improvement in the estimated mean change from baseline in SF-36 based on all observed data for the PCS and MCS component of SF-36. Further, all individual components of SF-36 were nominally significantly improved comparing CZP relative to placebo (Table 38). At Week 52, there were nominally significantly trends of improvement in the PCS component comparing CZP arm and placebo albeit the potential for bias due to differential discontinuation to OL CZP and patient and investigator knowledge of treatment received, there were numerical trends towards improvement in all components PCS of SF-36 with nominally significant difference being driven by the component of General Health. Numerical trends were observed for the MCS component of SF-36.

Table 38. SF-36 and its Components at Week 12 based on Observed Data Collected

	PBO Mean (SD) (N=158)	CZP Mean (SD) (N=159)	PBO Mean Change from baseline (SD)	CZP Mean Change from baseline (SD)	Est Diff (95% CI) p-value
SF-36 PCS	36.1 (7.8) (n=155)	42.6 (8.5) (n=155)	2.3 (6.1) (n=154)	8.1 (7.4) (n=153)	6.0 (4.5, 7.4) <0.001
Bodily Pain	36.6 (7.4) (n=155)	43.3 (8.6) (n=155)	2.7 (6.6) (n=154)	10.1 (8.1) (n=153)	7.2 (5.6, 8.7) <0.001
General Health	37.5 (8.7) (n=155)	43.3 (9.0) (n=155)	1.1 (6.8) (n=154)	5.1 (7.6) (n=153)	4.4 (2.9, 6.0) <0.001
Physical Function	38.4 (10.0) (n=155)	44.2 (9.2) (n=155)	2.9 (7.8) (n=154)	7.7 (8.4) (n=153)	5.2 (3.5, 6.9) <0.001
Role-Physical	36.2 (8.1) (n=155)	41.7 (8.5) (n=155)	1.6 (6.9) (n=154)	6.5 (8.0) (n=153)	5.2 (3.7, 6.8) <0.001
SF-36 MCS	43.3 (10.8) (n=155)	46.3 (10.5) (n=155)	2.0 (7.8) (n=154)	4.6 (9.6) (n=153)	2.8 (1.0, 4.6) 0.002
Mental Health	40.9 (10.7) (n=155)	45.2 (9.8) (n=155)	1.3 (8.0) (n=154)	6.1 (9.3) (n=153)	4.7 (2.9, 6.5) <0.001
Role-Emotional	42.5 (10.8) (n=155)	45.5 (10.5) (n=155)	2.0 (10.0) (n=154)	4.0 (9.8) (n=153)	2.6 (0.7, 4.6) 0.01
Social Function	40.4 (10.1) (n=155)	44.5 (9.4) (n=155)	3.6 (8.9) (n=154)	6.9 (8.8) (n=153)	3.8 (2.0, 5.6) <0.001
Vitality	39.9 (9.3) (n=155)	45.5 (9.8) (n=155)	3.0 (6.9) (n=154)	7.0 (9.3) (n=153)	4.5 (2.7, 6.2) <0.001

1: Difference in means comparing CZP with PBO, respective 95% CI, based on Reviewer's analysis using a linear regression adjusting for stratification factors, baseline covariate of interest, and treatment, assuming homoskedasticity between treatment groups.
Abbreviations: SF-36=Short-Form 36-Item Health Survey; PCS=Physical Component Summary; MCS=mental component summary; PBO=placebo; CZP=certolizumab pegol; SD=standard deviation; CI=confidence intervals; n=number of patients with observed efficacy data
[Source: Statistical Reviewer]

Clinical Reviewer's comments: It should be noted that SF-36 was not on the hierarchical testing sequence. (b) (4)

(b) (4)

Additional Analyses Conducted on the Individual Trial

The sample estimates of treatment effect in ASDAS-MI response at Week 52 among subgroups (specifically, age, gender, race, region, MRI/CRP classification, and HLA-B27 status) were based on a logistic regression adjusting for treatment effect. There was likely some random highs and

random lows in sample estimates of subgroup treatment effects due to small sample size and large variability for some subgroups. To quantitatively address the random highs and random lows, we included shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates, i.e., the estimated log-odds of ASDAS-MI response comparing CZP with placebo, is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. Consequently, sample estimate is "shrunk" towards the overall estimate.

The Bayesian hierarchical model assumptions are:

For i = 1, 2… Y_i represents the estimated log odds of ASDAS-MI response in a subgroup level i, assume Yi approximately $N(\mu i, \sigma i^2)$ where

- σ_i^2 are the estimated variance of the log odds of ASDAS-MI response in subgroup level i
- $\mu_i \sim N(\mu, \tau_2)$
- $\mu \sim N(0, 16)$, $1/\tau_2 \sim$ Gamma(0.01, 0.01)

Here we used the same flat prior to derive shrinkage estimates for all subgroups.
The results of the sample estimates and the shrinkage estimates of treatment effects in the same subgroups, are presented in Table 39 and Table 40.

The sample size was not sufficient to conduct multi-way subgroup analyses. Therefore, results were presented for marginal subgroups. Bayesian hierarchical model was not evaluated for subgroups that had 0% response on one arm. In summary, subgroups analysis by demographic subgroups were consistent with findings in the overall population, based on ASDAS-MI response at Week 52 and remaining on study and on randomized treatment.

Table 39. Subgroup Analysis for Gender, Race, Age, and Region at Week 52 for ASDAS-MI Responders

	n	PBO Responses (%)	n	CZP 200 mg SC Q2W Responses (%)	OR 95% CI[1]	Shrinkage Estimates 95% PI
Overall	158	11 (7%)	159	75 (47%)	11.9 (6.0, 23.7) [2]	
Age: 18 - 45	119	11 (9.2%)	125	65 (52.0%)	10.6 (5.2, 21.8)	NA
Age: ≥45 years	39	0 (0.0%)	34	10 (29.4%)	(4.2, -) [3]	NA
Gender: Male	76	7 (9.2%)	78	47 (60.3%)	14.9 (6.0, 37.0)	13.5 (6.2, 30.1)
Gender: Female	82	4 (4.9%)	81	28 (34.6%)	10.3 (3.4, 31.3)	11.5 (4.4, 27.5)
Race: White	148	10 (6.8%)	152	73 (48.0%)	12.8 (6.2,26.2)	11.8 (5.9, 24.0)
Race: Non-White	10	1 (10.0%)	7	2 (28.6%)	3.6 (0.2, 63.4)	8.4 (0.7, 35.1)
Region: North America	13	0 (0.0%)	15	2 (13.3%)	(0.25, -) [3]	NA
Region: Outside of North America	145	11 (7.0%)	144	73 (50.7%)	12.5 (6.2, 25.2)	NA

1: Stratified logistic regression was fit to the primary composite endpoint adjusting for treatment only. Differed from the Applicant analysis where regression model included interaction of subgroup and treatment for some models.
2: Logistic regression was fit to the primary composite endpoint adjusting for treatment only. Differed from the Applicant analysis where regression model further adjusted for region and MRI/CRP classification.
3: Because there were 0 responders in the PBO, the OR is infinity, the upper limit is also infinity. Therefore, the 95% lower limit is reported to reflect the uncertainty we have in the subgroup category based on exact test using PROC FREQ.
Abbreviations: PBO=placebo; CZP=certolizumab pegol; SC=subcutaneously Q2W=every two weeks; OR=odds ratios; CI=confidence intervals; PI=prediction intervals
[Source: Statistical Reviewer]

In summary, subgroup analysis by disease characteristics of interest subgroups were consistent with findings in the overall population, based on ASDAS-MI response at Week 52 and remaining on study and on randomized treatment, albeit the sample sizes within each subgroup categories were small. Post-hoc subgroup analysis conducted by the reviewer based on differences in proportions for the primary endpoint and ASAS40 at week 52 were also consistent with findings in the overall population (Figure 10).

Table 40. Subgroup Analysis for MRI/CRP Classification, and HLA-B27 Status at Week 52 for ASDAS-MI Responders

	n	PBO Responses (%)	n	CZP 200 mg SC Q2W Responses (%)	OR 95% CI [1]	Shrinkage Estimates 95% PI
Overall	158	11 (7%)	159	75 (47%)	11.9 (6.0, 23.7) [2]	
MRI-/CRP+	40	5 (12.5%)	40	19 (47.5%)	7.0 (2.2, 22.8)	9.1 (3.0, 22.2)
MRI+/CRP-	76	3 (3.9%)	74	22 (29.7%)	10.9 (3.0, 39.3)	11.4 (4.1, 29.8)
MRI+/CRP+	42	3 (7.1%)	45	34 (75.6%)	42.5 (10.5, >100)	19.0 (7.0, 81.5)
Positive HLAB27	133	11 (8.3%)	128	68 (53.1%)	13.6 (6.6, 27.9)	NA
Negative HLAB27	25	0 (0.0%)	31	7 (22.6%)	(1.73, -) [3]	NA

1: Stratified logistic regression was fit to the primary composite estimand adjusting for treatment only. Differed from the Applicant analysis where regression model included interaction of subgroup and treatment.
2: Logistic regression was fit to the primary composite endpoint adjusting for treatment only. Differed from the Applicant analysis where regression model further adjusted for region and MRI/CRP classification.
3: Because there were 0 responders in the PBO, the OR is infinity, the upper limit is also infinity. Therefore, the 95% lower limit is reported to reflect the uncertainty we have in the subgroup category based on exact test using PROC FREQ.
Abbreviations: PBO=placebo; CZP=certolizumab pegol; SC=subcutaneously Q2W=every two weeks; OR=odds ratios; CI=confidence intervals; PI=prediction intervals
[Source: Statistical Reviewer]

Statistical Issues in AS0006

During the review of this application, the statistical reviewer identified the following review issues

- Impact of patients crossing over to use of open label CZP

Study AS0006 allowed patients to receive either open label CZP or other biologics at the discretion of the Investigator after Week 12. There were major issues interpreting results at time points after Week 12, given that 61% of the placebo patients and 13% of the CZP patients had initiated open label CZP prior to Week 52 at the discretion of the Investigator. The Applicant had specified the composite estimand of interest in the SAP for the primary endpoint and key secondary responder-type endpoints and used non-responder imputation for patients who had missing evaluations or had initiated open label CZP prior to Week 52. Since the results based on the composite estimand could be driven by the disproportionate use of open label CZP across arms and potential knowledge of the treatment, the interpretation of a treatment policy estimand using all observed data at Week 52 to evaluate the signs and symptoms based on patient reported or physician reported outcomes regardless of adherence to randomized treatment or use of open label CZP is difficult. Differences in efficacy comparing CZP and placebo using the observed data collected could be impacted by differential rates of CZP use, or investigators' expectations of what works, rather than actual treatment differences if patients and investigators remained on blinded randomized treatment at Week 52 .

Therefore, the statistical reviewer focused on results for important continuous endpoints at Week 12 prior to initiation of open label CZP, at which time the assessment is considered more reliable. The Applicant's analyses of binary response endpoints, where patients who started open label CZP or discontinued randomized treatment and remained in the study were treated as non-responders, may be considered for inclusion in the labeling, given that these can be interpreted as evaluating a composite outcome defined by remaining on randomized treatment and achieving a response at the time point of interest. (b) (4) (b) (4) this was not considered appropriate because it relies on strong and untestable assumptions and does not appropriately account for the statistical uncertainty in the imputation.

- Primary multi-component endpoint ASDAS-MI

The primary endpoint of ASDAS-MI was assessed at Week 52 such that patients who discontinued treatment or withdrew from the study prior to Week 52 were considered non-responders. Therefore, it is difficult to determine whether observed treatment differences are due to treatment effects on patient signs and symptoms or due to differences in the proportion of patients on originally randomized treatments. A disproportionate amount of patients switched to open label CZP and were therefore imputed as non-responders in the primary analysis. The efficacy assessments for these patients were also limited later in the study although the Week 52 assessments were conducted.

Furthermore, because ASDAS-MI itself is a multi-component endpoint, it is also vital to understand whether the results were consistent across the individual components, and whether the individual component results were affected by the presence of missing data. Because there was differential use of open label CZP by arm, supportive results of the individual components were evaluated at Week 12 where initiation of open label CZP was low. Results for the individual components of ASDAS-MI at Week 12 were in general consistently in favor of the CZP arms.

Therefore, the efficacy of CZP 200 mg SC Q2W relative to placebo is convincing notwithstanding the differential rate of use of open label CZP.

- Subgroup analysis for MRI/CRP classification

Subgroup analyses were conducted by MRI/CRP classification using the primary composite estimand as well as the treatment policy estimand for ASDAS-MI at Week 52. Results in these subgroups were consistent with a trend of improvement in favor of CZP relative to placebo at Week 52.

- Evidence to support CZP 200 mg SC Q2W

There is statistical evidence of efficacy for the proposed CZP 200 mg SC Q2W dosing regimen over placebo based on the primary efficacy endpoint and key secondary endpoint in AS0006.

The estimated treatment effect size based on the composite estimand for ASDAS-MI at Week 52 was large and remained convincing even after sensitivity analyses, including tipping point analysis. In various supportive efficacy analyses, we included analyses where efficacy assessments based on patients entered OL CZP at Week 52 were used and the estimated difference in the proportion of patients with ASDAS-MI response at Week 52 was 16% (95%CI: 4.8%, 27.5%) comparing CZP with placebo arm on the absolute scale. The lower limit of the 95% CI is reasonably far away from null hypothesis of no difference. However, the impact of differential discontinuation, and knowledge of treatment could have impacted the outcome in evaluating the composite estimand regardless of adherence to randomized treatment. Therefore, supportive efficacy analyses were also conducted at earlier timepoints.

Trends of efficacy over time were observed at Week 12 when there were minimal discontinuations of randomized treatment to initiate open label CZP. There were significant improvements in other patient assessments (BASFI, BASMI, patient global), physician assessments, and patient reported outcomes. Supportive evidence of efficacy was also noted in study AS001 based on improvements of signs and symptoms using ASAS40 at Week 12 among patients who were centrally adjudicated as nr-axSpA. From an efficacy perspective, the Applicant's proposed 200 mg SC Q2W dose is reasonable.

In summary, the various sensitivity and tipping point analyses conducted to evaluate ASDAS-MI, ASAS40, and their components, and supportive analysis at various timepoints were generally supportive of the efficacy findings of an effect of CZP 200 mg SC Q2W compared to placebo. There were notabley increased rates of use of open label CZP differentially across arms (with more placebo patients discontinuing randomized treatment and starting open label CZP) after Week 12. The efficacy findings of a statistically significant effect of CZP relative to placebo were observed in both composite estimand and a conservative analysis using all observed data to target the treatment policy estimand for ASAS40 and ASDAS-MI at Week 52, albeit interpretation of the treatment policy estimand results are limited due to differential discontinuation across arms, patient's knowledge of open label treatment, expectation of benefit, and investigator's expectation of what works. To address concerns of potential bias induced in these analyses at Week 52, efficacy findings, conducted at earlier time points when initiation of open label CZP was minimal, were observed to have an effect on patient reported endpoints, comparing CZP 200 mg SC Q2W with placebo. Subgroup analysis by MRI/CRP classification was consistent with the primary analysis. Efficacy results from AS001, presented in the Section 8.1.4, based on patients who were centrally adjudicated to be nr-axSpA, were supportive of an observed effect in treatment of signs and symptoms using CZP 200 mg Q2W for patients with nr-axSpA.

8.1.3. AS001

AS001 was reviewed in detail with the first submission of Supplement 237. Please see the clinical review (by Dr. Janet Maynard) and the statistical review (by Dr. Yongman Kim) for

details regarding the study. Some parts of their review are presented again here, alongside the discussion and review from the clinical and statistical teams for this resubmission.

Trial Design

Basic Study Design

AS001 was a randomized, multi-center, placebo-controlled, parallel-group, 24-week double-blind study. The study included 5 periods. Figure 9. shows the study design of AS001 as a schematic diagram.

- **Period 1 (Screening Period):** 1 to 5 weeks utilized to obtain baseline laboratory data, to verify doses and stability of concomitant medications (MTX, SSZ, HCQ, NSAIDs, corticosteroids), to enable washout of any prohibited medications, and to permit initiation of any treatment necessary for LTBI
- **Period 2 (Double-Blind Treatment Period, DB1):** Week 0 to Week 24, double-blind, placeb-controlled

  Eligible patients were randomized to the following study treatments in a 1:1:1 ratio

  - CZP 400mg administered at Weeks 0, 2, and 4, followed by CZP 200mg Q2W (starting at Week 6)
  - CZP 400mg administered at Weeks 0, 2, and 4, followed by CZP 400mg Q4W (starting at Week 8)
  - PBO

  After completion of Period 2 (DB1), the database was locked, and the first interim CSR was written. Only a limited number of UCB personnel became unblinded for the purpose of data analysis. The Investigator and patient remained blinded.

  Escape: Patients receiving PBO who did not achieve at least a minimal response (defined as ASAS20) at both Weeks 14 and 16 were allocated to escape treatment from Week 16 onwards. Escape treatment entailed rerandomization in a 1:1 ratio to CZP 200mg Q2W or CZP 400mg Q4W. These patients continued this treatment for the duration of participation in the study. The Interactive Voice Response System was used to qualify patients for early escape at Week 16.
- **Period 3 (Dose-Blind Treatment Period, DB2):** Week 24 to Week 48, dose-blind for both patients and Investigators, no placebo

  Patients who completed 24 weeks of PBO treatment in Period 2 (DB1) were rerandomized in a double-blind manner in a 1:1 ratio to receive 3 loading doses of CZP 400mg at Weeks 24, 26, and 28 followed by CZP 200mg Q2W or CZP 400mg Q4W. Patients, who were originally randomized to CZP or escaped to CZP at Week 16, continued to receive the treatment they were receiving at Week 24.

After completion of Period 3 (DB2), the database was locked again, and the second interim CSR was written.

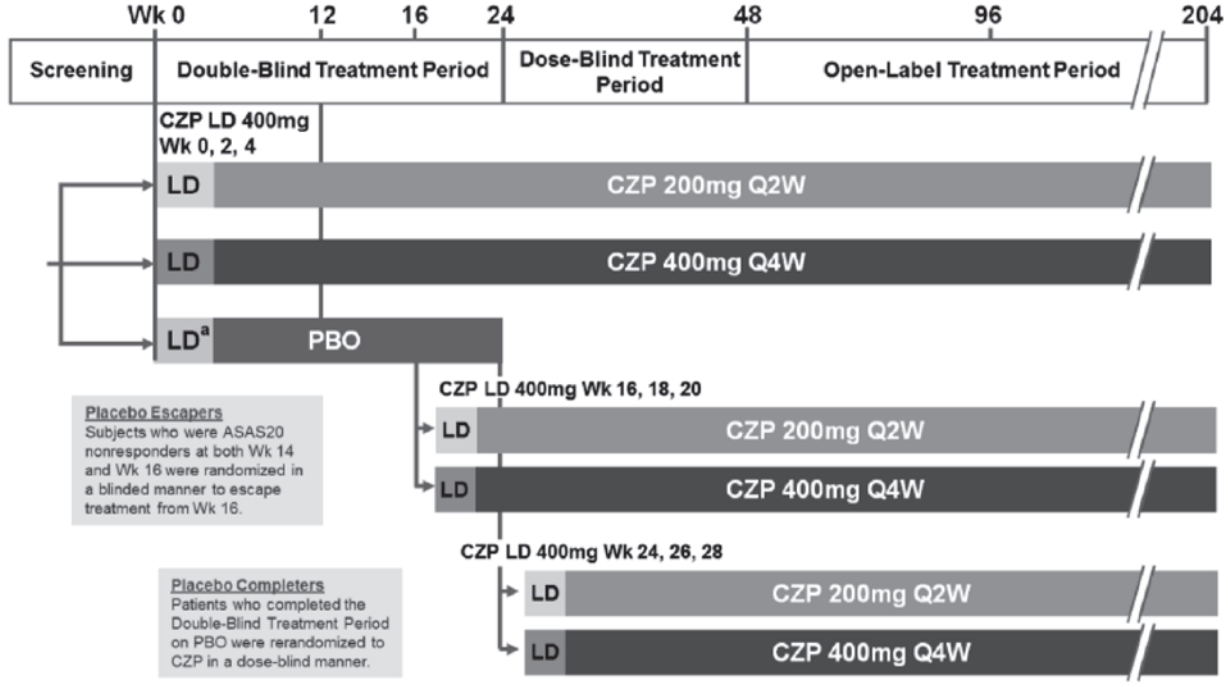
- **Period 4 (Open-Label Treatment Period, DB3):** Week 48 to Week 204, open-label

  Patients continued to receive the same dose regimen of CZP that they received during Period 3. Starting at Week 156, all patients visited the study site every 12 weeks. The last dosing visit was at Week 202 for the Q2W regimen and Week 200 for the Q4W regimen. The final study assessments were performed at Week 204.

- **Period 5 (Safety Follow-Up [SFU])**

  All patients, including those withdrawn from study treatment, had a SFU Visit 10 weeks after their last dose of study medication. The end of the study was defined as the date of the SFU Visit of the last patient in the study.

Figure 9. Study AS001 Schematic Diagram



ASAS20=Assessment of SpondyloArthritis international Society 20% response criteria; CZP=certolizumab pegol; LD=loading dose; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; Wk=Week
[a] Loading dose of placebo.

[Source: UCB, AS001 Final Clinical Study Report, Figure 3-1. Dated July 18, 2016: page 32.]

Key Inclusion/Exclusion Criteria

The patient population for study AS001 included patients with both AS and nr-axSpA. This review will focus on patients with nr-axSpA.

- Patients had to have a documented diagnosis of adult-onset axSpA of at least 3 months symptom duration as defined by the ASAS classification criteria. At least 50% of the study population should not have fulfilled the mNY classification criteria for the definite diagnosis of AS. Of the remaining patients with nr-axSpA, at least 50% had to meet ASAS imaging criteria (specifically, MRI), and the remainder could be enrolled based on the clinical criteria only.

Reviewer's comments: Dr. Maynard's clinical review indicated that both rheumatologists and radiologists reviewed x-rays and MRIs to document sacroiliitis.

- Patients had to have active disease as defined by each of the following:
    - BASDAI score ≥ 4
    - Spinal pain ≥ 4 on a 0 to 10 NRS (from BASDAI Item 2)
    - CRP > ULN and/or current evidence (i.e., within the last 3 months from Screening) for sacroiliitis on MRI as defined by ASAS classification criteria
- Patients had to have been intolerant to or have had an inadequate response to at least 1 NSAID.

AxSpA Disease-related Exclusions:

- Patients must not have had total spine ankylosis ("bamboo spine"), a diagnosis of any other inflammatory arthritis (e.g., RA, SLE), or a known diagnosis of fibromyalgia.
- Patients must not have had a secondary, noninflammatory condition (e.g., osteoarthritis) that, in the Investigator's opinion, was symptomatic enough to interfere with evaluation of the effect of study drug on the patient's primary diagnosis of axSpA.

In general, the other inclusion and exclusion criteria (permitted and prohibited concomitant medications, medical history exclusions, etc.) were similar to those in AS0006.

Clinical Reviewer's comments: In terms of the diagnosis of nr-axSpA and disease activity, there are some notable differences from study AS0006. First, diagnosis of nr-axSpA by not meeting mNY criteria for sacroiliitis on radiographs became an issue during the first submission and was part of the reason the indication for treatment of nr-axSpA received a Complete Response. In study AS001, patients were classified by the Investigator who performed a "local read" of historic x-rays (screening). Utilizing locally read radiographs to classify patients were the basis of enrollment and randomization of Supplement 237. Most randomized patients also had baseline x-rays that were centrally read by 2 independent reviewers. During the review of the first submission of Supplement 237, the review team noted that there was a number of misclassifications based on central evaluation, and the majority of the patients in study AS001 actually had AS. In study AS0006, the diagnosis of nr-axSpA was based on radiographs from within 12 months of baseline that were all centrally read. Also, symptom duration was 3 months in AS001 but 12 months in AS0006. Disease activity as measured by BASDAI and Spinal Pain was the same in both studies. However, the criterion for objective inflammation was different. In study AS001, in accordance with the ASAS criteria, patients had to have evidence of sacroiliitis on MRI and/or a current or historical CRP value above the upper limit of normal. In

study AS0006, the objectives signs of inflammation was based on MRI and/or CRP, specifically, the 3 possible categories of MRI+/CRP+, MRI+/CRP-, and MRI-/CRP+. These 3 subgroups of inflammation were felt to encompass the nr-axSpA population that would benefit most from anti-TNF therapy. These differences in the patient population were made to address Agency concerns raised during the original review of Supplement 237 leading to the Complete Response. Because of these differences, this review will focus on the efficacy data of patients with nr-axSpA (based on central reads) with objective inflammation from study AS001 to support study AS0006.

Dose selection

Study AS001 evaluated 2 different dosing regimens (200 mg Q2W and 400 mg Q4W) following the loading dose. The doses selected were based on the doses approved for the treatment of patients with RA. The loading dose regimen optimized the speed of onset, and the cumulative doses administered over time were the same for both dosing frequencies. UCB noted that other approved SC anti-TNF agents have utilized similar dosing regimens for AS and RA.

Assignment to treatment

An interactive voice response system was used for patients registration as well as randomization and treatment administration. Randomization was performed centrally. Patients were allocated to treatment in a 1:1:1 ratio (CZP 200 mg Q2W: CZP 400 mg Q4W: PBO), and randomization was stratified by site, fulfillment of mNY classification criteria, and prior anti-TNF exposure. PBO patients who escaped were rerandomized at Week 16 in a 1:1 ratio (CZP 200 mg Q2W: CZP 400 mg Q4W) stratified by fulfillment of mNY classification criteria and prior anti-TNF exposure.

Study Endpoints

The primary endpoint for AS001 was the proportion of ASAS20 responders at Week 12. An ASAS20 response was defined as an improvement of at least 20% and absolute improvement of at least 1 unit on a 0 to 10 numerical rating scale (NRS) in at least 3 of the 4 following domains: patient's global assessment of disease activity, pain assessment (total spinal pain), BASFI, and inflammation (average of the BASDAI questions 5 and 6 concerning morning stiffness intensity and duration) and the absence of deterioration in the potential remaining domain (deterioration is defined as a relative worsening of at least 20% and an absolute worsening of at least 1 unit).

Secondary endpoints with multiplicity adjustment plan included ASAS20 responses at Week 24, change from baseline in BASFI to Weeks 12 and 24, change from baseline in BASDAI to Weeks 12 and 24, change from baseline in BASMI to Weeks 12 and 24.

Other secondary endpoints pertinent to this resubmission included ASAS20, ASAS40, and ASAS5/6[20] response at multiple time points (Week 12 and 24) up to Week 48.

The statistical review for this study was conducted by Dr. Kim at the time of Supplement 237's first submission. For additional details regarding the study endpoints and the SAP, please see Dr. Kim's review.

Protocol Amendments

Please see Dr. Maynard's clinical review from the original submission for Supplement 237 for details regarding the protocol amendments.

8.1.4. AS001: Study Results

Compliance with Good Clinical Practices

Study AS001 was conducted in compliance with good clinical practice (GCP) guildlines. See Dr. Maynard's review for details.

Financial Disclosure

UCB's financial disclosures for study AS001 was reviewed by Dr. Maynard. No potentially conflicting financial interests were identified.

Patient Disposition

A total of 325 patients, recruited from 128 participating sites (North America, Latin America, Western Europe, and Central/Eastern Europe), were randomized to placebo (n=107), CZP 200 mg SC Q2W (n=111), or CZP 400 mg every four weeks (Q4W) (n=107). Randomization was stratified by site, fulfillment of modified New York criteria according to local interpretation of screening sacroiliac X-rays, and prior anti-tumor necrosis factor alpha (anti-TNFα) exposure.

Importantly, as previously noted, during the review of the original submission of this supplement, UCB identified some discrepancies in the reads of screening and baseline radiographs. First, not every patient who had a screening radiograph had a subsequent baseline radiograph. Of those who did, there were differences between the local read of screening x-rays and the central read of baseline x-rays. Table 41 shows the difference between the numbers of patients who were classified as being mNY-positive or mNY-negative based on the local or central read. Thus, based on local assessment of screening radiographs,

[20] At least 20% improvement in 5 of 6 domains of ASAS response, including spinal mobility (i.e., lateral spinal flexion, BASMI) and CRP as more objective measures

there were 147 patients with nr-axSpA, whereas, based on the central assessment of baseline radiographs, 98 patients had nr-axSpA.

Table 41. Comparison of Investigator (Local) and Central Read of Sacroiliac X-rays

Investigator's assessment (screening)	Central reader's assessment (baseline)†		
	mNY-Yes n (%)	mNY-No n (%)	Total N
mNY-Yes (N=178)	112 (79)	29 (21)	141
mNY-No (N=147)	72 (51)	69 (49)	141

† Central reads were not performed for 43 patients as x-rays were not available. Of the 43 patients, 37 had been classified as AS by the Investigator and 6 had been classified as non-radiographic axial SpA by the Investigator
mNY=modified New York Criterion
Yes=fulfilling modified New York Criterion for ankylosing spondylitis
No=not fulfilling the modified New York Criterion for ankylosing spondylitis
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 7-11, page 135

[Source: Dr.Janet Maynard's Primary Clinical Review of the Original Submission of S237, Table 21. 2013, page 56.]

Clinical Reviewer's comments: For the purposes of this review, the data of the patients with nr-axSpA will be reviewed utilizing the patients who were determined to have nr-axSpA based on both centrally read baseline radiographs. This would be consistent with the methods of study AS0006 for which all imaging were centrally read. For details of the nr-axSpA population categorized by the locally read screening radiographs, please see Dr. Maynard's clinical review from the time of the original submission.

Based on the local read, a total of 147 patients with nr-axSpA were randomized to receive PBO (n=50), CZP 200mg Q2W (n=46), and CZP 400mg Q4W (n=51). Utilizing the centrally read baseline radiographs, 98 patients with nr-axSpA were randomized to the PBO arm (n=35), CZP 200mg Q2W (n=33), and CZP 400mg Q4W (n=30). The patient disposition of this nr-axSpA population in study AS001 is described in the Table 42. More than half of the PBO patients (n=20) escaped and were re-randomized to CZP 200mg Q2W (n=9) and CZP 400mg Q4W (n=11). Only 10 patients (66.7%) remained on PBO at Week 24. Greater proportion of patients completed the study to Week 24 on CZP (93.9% on CZP 200mg Q2W and 83.3% on CZP 400mg Q4W).

Table 42. Patient Disposition through Week 24 in Study AS001 (nr-axSpA population†)

	PBO	CZP 200mg Q2W	CZP 400mg Q4W
Randomized, n	35	33	30
Escaped, n	20 (9 CZP 200mg Q2W; 11 CZP 400mg Q4W)	--	--
Completed 24 weeks, n	28 (80%) [1]	31 (94%)	25 (83%)
Discontinued, n(%)	7 (20%) [2]	2 (6%)	5 (17%)

†Patients are classified as nr-axSpA based on centrally read baseline radiographs
1: A total of 10, 8, and 10 patients on placebo, placebo escaped to CZP 200 mg, and placebo escaped to CZP 400 mg completed the 24 weeks period.
2: A total of five, one, and one patients on placebo, placebo escaped to CZP 200 mg, and placebo escaped to CZP 400 mg discontinued.
Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks
[Source: UCB response to clinical IR, dated June 13, 2013, Table 8, page 13, Table 1.2.3.1 in tables-resp3-fda-axspa-clinical.pdf]

Table of Demographic Characteristics

Dr. Maynard's review details the baseline demographics of all patient populations categorized by local read. In this review, the demographics of the nr-axSpA population (as categorized by the centrally read baseline radiographs) are reviewed.

Table 43 presents the baseline demographics of the nr-axSpA population. The patient characteristics were similar across treatment arms with a mean age between 39-40. There was a slightly greater proportion of females to males in the PBO and CZP 200mg Q2W arms, which is consistent with the general demographics of this patient population. In the CZP 400mg Q4W arm, there was a slightly larger proportion of males. The majority of patients were white.

Table 43. Baseline Demographics of nr-axSpA Population† in Study AS001

	PBO N=35	CZP 200mg Q2W N=33	CZP 400mg Q4W N=30
Age (years)[1]			
Mean (SD)	41 (13.3)	39 (13.8)	40 (11.6)
Median (range)	43 (19 - 68)	36 (20 - 78)	40 (19 - 67)
Gender, n (%)			
Male	15 (43%)	13 (39%)	16 (53%)
Female	20 (57%)	20 (61%)	14 (47%)
Race, n (%)			
White	29 (83%)	29 (88%)	26 (87%)
Black	1 (3%)	0	1 (3%)
Asian	0	0	0
American Indian/Alaskan Native	1 (3%)	1 (3%)	0
Other/missing	1 (3%)/3 (9%)	0/3 (9%)	2 (7%)/1 (3%)
Weight (kg) [1]	84 (17.5)	78 (20.6)	88 (22.5)
Height (cm) [1]	172 (9.0)	170 (7.2)	170 (9.9)

†Patients are classified as nr-axSpA based on centrally read baseline radiographs
1: Mean and standard deviations are presented.
Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks; SD=standard deviation
[Source: UCB response to clinical IR, dated June 13, 2013, Table 6, page 10-11, Table 2.1.12 in tables-resp3-fda-axspa-clinical.pdf.]

Clinical Reviewer's comments: In general, these baseline demographics are very similar to the demographics of the patients in study AS0006. The mean age in study AS001 is slightly higher than the age in study AS0006, which was 37 years in all treatment arms.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline disease characteristics were similar across treatment arms for nr-axSpA patients in study AS001. Table 44 shows these disease characteristics. The mean time since diagnosis was 4.55 year for the PBO arm, 3.85 years for the CZP 200mg Q2W arm, and 6.86 years for the CZP 400mg Q4W arm. The mean duration of back pain was 8-10 years. The majority of patients (62.9% for PBO, 60.6% for CZP 200mg Q2W, 66.7% for CZP 400mg Q4W) were HLA-B27 positive. The baseline BASDAI, BASMI, and BASFI disease activity scores were similar for all treatment groups.

Table 44. Baseline Disease Characteristics of nr-axSpA Population† in Study AS001

	PBO N=35	CZP 200mg Q2W N=33	CZP 400mg Q4W N=30
Time since diagnosis (years)			
Mean (SD)	4.55 (5.21)	3.85 (4.62)	6.86 (7.22)
Median (range)	3.10 (0-24.2)	2.05 (0.1-19.5)	5.02 (0.2-25.3)
Symptom (back pain) duration (years)			
Mean (SD)	10.0 (11.0)	7.7 (7.1)	10.7 (8.7)
Median (range)	4.6 (0.5-41.5)	4.3 (0.5-23.4)	11.4 (0.3-25.6)
CRP (mg/L), mean (SD)	15.7 (13.4)	13.7 (14.6)	15.6 (28.9)
Testing for HLA-B27, n (%)			
Negative	13 (37.1)	11 (33.3)	8 (26.7)
Positive	22 (62.9)	20 (60.6)	20 (66.7)
Baseline BASDAI scores, FAS, mean (SD)	6.4 (1.5)	6.3 (1.5)	6.6 (1.4)
Baseline BASMI scores, FAS, mean (SD)	3.3 (1.4)	3.2 (1.4)	3.4 (1.8)
Baseline BASFI scores, FAS, mean (SD)	5.1 (2.3)	4.9 (2.3)	5.0 (2.5)

†Patients are classified as nr-axSpA based on centrally read baseline radiographs
Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks; SD=standard deviation
[Source: UCB response to clinical IR, dated June 13, 2013, Table 7, page 12-13.]

Clinical Reviewer's comments: The baseline disease characteristics of mean CRP, time since diagnosis (disease duration), and symptom duration (specifically, back pain) were similar to the baseline disease characteristics of patients in study AS0006. Additionally, baseline BASDAI, BASMI, and BASFI scores were similar. The only difference was HLA-B27 positivity. Study AS0006 had a higher proportion (81-84% across treatment arms) of HLA-B27 positive patients compared to study AS001 (60-66% across treatment arms).

Unlike study AS0006, patients did not have to have objective inflammation defined by the presence of MRI imaging consistent with sacroiliitis and/or elevated CRP. Enrolled patients had to fulfill ASAS criteria and had to evidence of active disease (as measured by current or historical elevation in CRP and/or MRI). Thus, an MRI was not mandatory for all patients. The Applicant did perform an analysis of the nr-axSpA population and determined the number of patients who could be classified as MRI+/CRP+, MRI+/CRP-, and MRI-/CRP+. Additionally, the Applicant notes that some patients, who were originally classified as mNY+ by local reading of screening x-rays, could potentially fall into a category of MRI-/CRP-. Table 45 displays the MRI/CRP status at baseline for the nr-axSpA population in study AS001. In all treatment arms, a greater proportion of patients was MRI-/CRP+ (40.0% in the PBO arm, 39.4% in the CZP 200mg Q2W arm, 60.0% in the CZP 400mg Q4W arm). The lowest proportion of patients was MRI+/CRP+.

Table 45. Baseline MRI/CRP Status for nr-axSpA† Population in Study AS001

	PBO N=35 n (%)	CZP 200mg Q2W N=33 n (%)	CZP 400mg Q4W N=30 n (%)
MRI+/CRP+	11 (31.4)	8 (24.2)	6 (20.0)
MRI+/CRP-	6 (17.1)	4 (12.1)	3 (10.0)
MRI-/CRP+	14 (40.0)	13 (39.4)	18 (60.0)
MRI-/CRP-	0	5 (15.2)	2 (6.7)
MRI not available/CRP+	4 (11.4)	3 (9.1)	1 (3.3)

†Patients are classified as nr-axSpA based on centrally read baseline radiographs
Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks; SD=standard deviation; MRI=magnetic resonance imaging; CRP=C-reactive protein
[Source: UCB response to clinical IR, dated February 7, 2019, Table 2, page 3.]

Clinical Reviewer's comments: The categorization of MRI/CRP status differed in study AS001 and AS0006. In study AS001, overall most patients (46%) were MRI-/CRP+ compared to 13% MRI+/CRP- and 26% MRI+/CRP+. In study AS0006, most patients (46%) were MRI+/CRP- compared to 24% MRI-/CRP+ and 30% MRI+/CRP-.

Table 46 shows the proportion of nr-axSpA patients who were treated with NSAIDs, conventional DMARDs, and anti-TNF inhibitors prior to study AS001. The majority of all patients were treated with NSAIDs and was consistent with the inclusion criterion of intolerance or inadequate response to NSAIDs. Interestingly, more patients in the PBO arm had previously received DMARDs (specficially, MTX) and anti-TNF therapy compared to patients in the CZP arms. The number of patients who were previously treated with anti-TNF therapy was generally low for all patients.

Table 46. Prior Medication Use in the nr-axSpA Population† in Study AS001

	PBO N=35 n (%)	CZP 200mg Q2W N=33 n (%)	CZP 400mg Q4W N=30 n (%)
Any past NSAID use	29 (82.9)	25 (75.8)	21 (70.0)
Any prior DMARD use	17 (48.6)	9 (27.3)	11 (36.7)
Methotrexate/Methotrexate sodium	10 (28.6)/0	3 (9.1)/0	4 (13.3)/1 (3.3)
Azathioprine	0	1 (3.0)	1 (3.3)
Leflunomide	2 (5.7)	0	0
Cyclophosphamide	0	1 (3.0)	0
Chloroquine	1 (2.9)	0	0
Cyclosporine	1 (2.9)	0	0
Sulfasalazine	10 (28.6)	6 (18.2)	6 (20.0)
Other/uncoded	0/1 (2.9)	0/0	0/0
Anti-TNFα inhibitor	9 (25.7)	2 (6.1)	2 (6.7)
Opioid analgesics*	N/A	N/A	N/A

†Patients are classified as nr-axSpA based on centrally read baseline radiographs
*UCB did not proactively collect past opioid use during study AS001.
Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks; NSAID=nonsteroidal anti-inflammatory drug; DMARD=disease-modifying antirheumatic drug; TNF=tumor necrosis factor
[Source: UCB response to clinical IR, dated June 13, 2013, Table 3, page 5-6.]

Table 47 shows the proportion of nr-axSpA patients who utilized concomitant NSAIDs, MTX/SSZ, and anti-TNF inhibitors during the course of the study. The patients who received another anti-TNF inhibitor were patients who terminated early from the study. The proportion of patients using NSADIs was slightly lower in the PBO arm (74.3% vs. 81.8% in the CZP 200 mg Q2W arm and 83.3% in the CZP 400 mg Q4W arm). On the other hand, concomitant DMARD use was slightly higher in the PBO arm and lowest in the CZP 200 mg Q2W arm.

Table 47. Concomitant Medication Use in nr-axSpA Population† in Study AS001

	PBO N=35 n (%)	CZP 200mg Q2W N=33 n (%)	CZP 400mg Q4W N=30 n (%)
Any concomitant NSAID use	26 (74.3)	27 (81.8)	25 (83.3)
Any concomitant DMARD use	16 (45.7)	8 (24.2)	10 (33.3)
Methotrexate/Methotrexate sodium	8 (22.9)/1 (2.9)	3 (9.1)/0	7 (23.3)/0
Sulfasalazine	7 (20.0)	5 (15.2)	5 (16.7)
Anti-TNFα inhibitor	1 (2.9)	0	1 (3.3)
Opioid analgesics	11 (31.4)	10 (30.3)	7 (23.3)

†Patients are classified as nr-axSpA based on centrally read baseline radiographs
Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks; NSAID=nonsteroidal anti-inflammatory drug; DMARD=disease-modifying antirheumatic drug; TNF=tumor necrosis

factor
[Source: UCB response to clinical IR, dated June 13, 2013, Table 3, page 5-6.]

Clinical Reviewer's comments: The use of baseline and concomitant medications were similar between studies AS001 and AS0006.

Efficacy Results Relevant as Supporting Evidence

To support the efficacy results from AS0006, the ASAS20 and ASAS40 response at Week 12 were re-assessed. Again, emphasis is placed on the patient population categorized as nr-axSpA by centrally read baseline radiographs. P-values included in this section are unadjusted for multiplicity of subgroups and thus should be interpreted with caution.

The results for ASAS40 at Week 12 were reported for patients ascertained as nr-axSpA using local readers for x-rays, central readers for x-ray, and concordant local and central readers for X-ray (Table 48). The probability of ASAS40 response for patients randomized to either doses of CZP were numerically similar in each of the different x-ray classification. Among patients with centrally-read baseline radiographs, the estimated difference in the probability of ASAS40 response at Week 12 on randomized treatment and remaining in the study comparing all randomized CZP patients on either doses with all randomized placebo patients was 22% (95%CI: 6.2%, 43%; p-value=0.009).

Table 48. ASAS40 Response at Week 12 for nr-axSpA Population in Study AS001

	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200 mg Q2W + CZP 400 mg Q4W[1]
Locally-read Screening Radiographs, N	**N=50**	**N=46**	**N=51**	**N=97**
ASAS40 Responders, n (%)	8 (16%)	22 (48%)	24 (47%)	46 (47%)
Difference to PBO (%)	--	32	22.7	31
95% CI	--	(14%, 49%)	(14%, 48%)	(17%, 46%)
p-value		0.067	0.021	<0.001
Centrally-read Baseline Radiographs, N	**N=35**	**N=33**	**N=30**	**N=63**
ASAS40 Responders, n (%)	4 (11%)	10 (30%)	11 (37%)	21 (33%)
Difference to PBO (%)	--	19	25	22%
95% CI	--	(-0.01%, 38%)	(5%, 45%)	(6.2%,43%)
p-value	--	0.056	0.018	0.009
Concordant Locally-read and Centrally-read Radiographs, N	**N=29**	**N=23**	**N=17**	**N=40**
ASAS40 Responders, n (%)	4 (14%)	9 (39%)	6 (35%)	15 (38%)
Difference to PBO (%)	--	25	21	24
95% CI	--	(2%, 49%)	(-5%, 47%)	(4%, 43%)
p-value	--	0.042	0.0118	0.022

1: Results were reported by the Statistical Reviewer.
Treatment differences (and correspond 95% CIs and p-values) are based on difference in proportions, 95% CI based on normal approximation to difference in proportions, and p-value from the Wald-based test.
Abbreviations: PBO=placebo; CZP=certolizumab pegol; SC=subcutaneously Q2W=every two weeks; Q4W=every four weeks; CI=confidence intervals; ASAS=Assessment of SpondyloArthritis international Society
[Source: UCB response to clinical IR, dated February 4, 2019, Table 1, page 3.]

In study AS001, 42% and 47% of the patients with centrally-read baseline radiographs randomized to CZP 200 mg Q2W and 400 mg Q4W respectively and 20% of the patients with centrally-read baseline radiographs randomized to placebo achieved a ASAS20 response and remained in the study on randomized treatment (Table 49). Among nr-axSpA patients defined by centrally read baseline radiographs, the difference in probability of ASAS20 response was 22.4% significantly higher in the CZP 200mg Q2W arm (95% CI: 1%, 44%; p=0.046) and 26.7% significantly higher in the CZP 400mg Q4W (95% CI; 4%, 49%; p=0.023) arm compared to placebo arm, on an absolute scale.

Table 49. ASAS20 Response at Week 12 for nr-axSpA Population in Study AS001

	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200 mg Q2W + CZP 400 mg Q4W[1]
Locally-read Screening Radiographs, N	**N=50**	**N=46**	**N=51**	**N=97**
ASAS20 Responders, n (%)	20 (40%)	27 (59%)	32 (63%)	59 (61%)
Difference to PBO (%)	--	19	23	21
95% CI	--	(-1%, 38%)	(4%, 42%)	(4%, 38%)
p-value		0.067	0.021	0.016
Centrally-read Baseline Radiographs, N	**N=35**	**N=33**	**N=30**	**N=63**
ASAS20 Responders, n (%)	7 (20%)	14 (42%)	14 (47%)	28 (44%)
Difference to PBO (%)	--	22	27	24
95% CI	--	(1%, 44%)	(4%, 49%)	(6%, 43%)
p-value	--	0.046	0.023	0.011
Concordant Locally-read and Centrally-read Radiographs, N	**N=29**	**N=23**	**N=17**	**N=40**
ASAS20 Responders, n (%)	7 (24%)	11 (48%)	7 (41%)	18 (45%)
Difference to PBO (%)	--	24	17	22
95% CI	--	(-2%, 49%)	(-11%, 45%)	(6%, 38%)
p-value	--	0.080	0.248	0.009

1: Results were reported by the Statistical Reviewer.
Treatment differences (and correspond 95% CIs and p-values) are based on difference in proportions, 95% CI based on normal approximation to difference in proportions, and p-value from the Wald-based test.
Abbreviations: PBO=placebo; CZP=certolizumab pegol; SC=subcutaneously Q2W=every two weeks; Q4W=every four weeks; CI=confidence intervals; ASAS=Assessment of SpondyloArthritis international Society
[Source: UCB response to clinical IR, dated February 4, 2019, Table 1, page 3.]

For other efficacy assessments from study AS001, please see the clinical and statistical reviews from the first submission of Supplement 237.

8.1.5. Assessment of Efficacy Across Trials

Assessment of efficacy across the two efficacy trials, AS0006 and AS001, is discussed in the section above. A discussion of how the data from both studies can be integrated to establish effectiveness of both maintenance doses of CZP is provided in the section below, Section 8.1.6.

8.1.6. Integrated Assessment of Effectiveness

UCB submitted the data from study AS0006, a 52-week, double-blind, placebo-controlled study with 317 patients with nr-axSpA, as the primary basis for the effectiveness of CZP for the treatment of nr-axSpA. This is a new study since the time of Complete Response. As further supportive evidence of effectiveness, UCB included data from study AS001, a 24-week, double-blind, placebo-controlled study with 98 patients with nr-axSpA (based on central read). This

was the original study submitted for this proposed indication that was given a Complete Response. Reviewed and considered together, both studies meet the statutory evidentiary standard for effectiveness.

Study AS006 adequately addressed the concerns from the Complete Response. The study was a double-blind, placebo-controlled study of 12-month duration. The ASAS classification criteria and the diagnosis of nr-axSpA are new, and the 52-week study could potentially allow for some understanding of the natural history of nr-axSpA. The longer duration would also be more informative in assessing the treatment benefit. Additionally, there was adequate representation of patients in each of the categories of inflammation, specifically, (+) MRI findings at the SI joints, elevated CRP at baseline, and both (+) MRI at SI joints and elevated CRP at baseline. These patients with objective inflammation are characterized with respect to disease activity and burden of disease to better inform the benefit risk assessment of treatment with certolizumab.

Given the duration of study AS0006, the protocol allowed for patients to transition from randomized treatment to other therapy. A large portion of PBO patients (61%) discontinued randomized treatment during the study and transitioned to open-label CZP. Only 13% of patients in the CZP arm discontinued randomized treatment. Most patients discontinued randomized treatment after Week 12 and prior to Week 24. Patients who discontinued randomized treatment underwent a different schedules of assessments compared to patients who stayed on randomized treatment. Thus, interpretation of the efficacy data from AS0006 was complicated and required different analyses by the statistical team.

The primary endpoint for study AS0006 was ASDAS-MI response at Week 52. There is no regulatory history of using ASDAS-MI for the treatment of axSpA, specifically AS. However, ASDAS is an accepted measure of disease activity by the community.[21,22] ASAS-EULAR concluded that ASDAS correlates well with patients' and physicians' level of disease activity, and it has a proven longitudinal relationship with subsequent syndesmophyte formation.[23] Based on a validated process, an ASDAS ≥ 2.1 is consistent with active disease, and an improvement of ≥ 1.1 is considered clinically important.[24] Thus, ASDAS-MI, which is a reduction of ASDAS ≥2, is a higher threshold and would be clinically meaningful. More patients on CZP 200mg Q2W (47%) compared to patients on PBO (7%) experienced a clinical response, and the difference was stastically significant ($p<0.001$). Utilizing various statistical methods, the primary endpoint showed a greater response in the CZP arm.

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[21] Ghosh N and Ruderman E. *Arthritis Res Ther*. 2017; 19: 286-295.
[22] Lockwood M and Gensler L. *Best Pract Res Clin Rheumatol*. 2017; 31: 816-829.
[23] Van der Heijde D, Ramiro S, Landewé R, et al. *Ann Rheum Dis*. 2017; 76:978-991.
[24] Ibid.

ASAS does have more regulatory precedent for the treatment of AS, a related condition. ASAS40 was a major secondary endpoint and was considered important for interpretation of the efficacy of CZP for nr-axSpA. At Week 52, there was a greater proportion of patients on CZP (56.6%) than patients on PBO (15.8%) who achieved ASAS40 response, and the difference was again statistically significant ($p<0.001$). Subgroup analyses, including the analysis of the different subgroups of inflammation (MRI+/CRP+, MRI+/CRP-, and MRI-/CRP+), were all consistent with the overall population.

Like ASAS, ASDAS-MI is a multi-component endpoint that differentially weights various endpoints evaluating the signs and symptoms of the disease, through patient reported outcomes and inflammation status. Therefore, the results of positive findings in ASDAS-MI would need to be supported by improvements in the individual components. In study AS0006, analyses of the individual components of both ASDAS and ASAS at earlier timepoints showed improvements relative to placebo, supportive of an effect of CZP over placebo based on ASAS and ASDAS-MI.

In summary, in study AS0006, the primary analysis, various sensitivity and tipping point analyses to evaluate ASDAS-MI, ASAS40, and their components, supportive analysis at various timepoints were generally supportive of the efficacy findings of an effect of CZP 200 mg SC Q2W compared to placebo (See Statistical Issues in AS0006). There were notable increased rates of use of OL CZP differentially across arms (with more placebo patients discontinuing randomized treatment and starting OL CZP) after Week 12, the efficacy findings of a statistically significant effect of CZP relative to placebo were observed in both composite estimand and a conservative treatment policy estimand for ASAS40 and ASDAS-MI at other weeks. To address concerns of potential bias induced by patient's knowledge of treatment, expectation of benefit, efficacy findings at earlier time point when initiation of OL CZP was minimal were observed to have an effect on patient reported endpoints, comparing CZP 200 mg SC Q2W with placebo. Albeit the potential bias due to OL use, potential differences in patient expectations due to differential rates of use across arms, or investigators' expectations of what works, rather than differences in drug effects, the study results were supportive of an observed effect in treatment of signs and symptoms using CZP 200 mg Q2W for patients with nr-axSpA.

The chronic dose of CZP 400 mg Q4W was not studied in AS0006. Instead, UCB relied on the data from AS001. At the time of original submission, it was determined that the number of patients with nr-axSpA, based on a central read of the baseline radiographs, was too small (N=98 with just 63 patients on CZP and 35 patients on PBO) and not sufficient as a single study to allow for a regulatory decision. However, it is adequate as a supportive study to AS0006 and to inform the proposed dosing regimen of CZP 400 mg Q4W. In general, the nr-axSpA population in study AS001 was similar to the population in AS0006. There was a slight difference in the category of objective inflammation at baseline with more patients in study AS001 classified as MRI-/CRP+ (46%) and more patients in study AS0006 classified as MRI+/CRP- (46%). Most patients on CZP (33.3%) had an ASAS40 response at Week 12 compared to

patients on PBO (11.4%). The ASAS40 response was similar for both doses of CZP (30.3% on 200 mg Q2W and 36.7% on 400 mg Q4W). Thus, the efficacy results for both doses of CZP from study AS001 support the results from study AS0006.

In conclusion, study AS0006 provides substantial evidence on the efficacy of CZP 200 mg Q2W and results from study AS001 were supportive of the efficacy of the CZP 400 mg Q4W (with the same loading dose of CZP 400 mg initially and Weeks 2 and 4) for the treatment of nr-axSpA with objective signs of inflammation.

8.2. Review of Safety

8.2.1. Safety Review Approach

For the overall safety in nr-axSpA, including serious adverse events (SAEs) and AEs leading to discontinuation, the focus of this review is the Applicant's primary safety pool, which consists of data from the placebo-controlled periods of AS0006 and AS001. This safety pool only includes patients who received PBO and CZP 200mg Q2W. In order to evaluate the safety of patients who received the 400mg dosing regimen, the safety from the placebo-controlled period of AS001 with both doses of CZP will also be evaluated separately.

For rarer safety events, such as the AEs of special interest (AESIs) for anti-TNFα inhibitors, both the primary and secondary safety pools are summarized. The secondary safety pools include all patients who have received CZP in AS001 and AS0006 as well as ongoing studies AS0005 and AS0007.

The safety pools are described in more detail below, Section 8.2.2.

8.2.2. Review of the Safety Database

Overall Exposure

UCB created 2 safety pools for the analyses of safety in nr-axSpA. The 4 studies included in these safety pools were AS0006, AS001, AS0005, and AS0007. Refer to Table 9 for details of the studies includes for the analyses of safety of CZP in patients with nr-axSpA. Of these 4 studies, only AS001 is completed. For study AS0006, the safety cutoff date was May 1, 2018. For studies AS0005 and AS0007, the safety cutoff date was February 19, 2018.

The primary safety pool (Pool S1) combined the data from the double-blind, placebo-controlled periods of AS001 (24 weeks) and AS0006 (52 weeks). Patients from AS001 were included in Pool S1 if they met AS0006 eligibility criteria, specifically, objective signs of inflammation (e.g., elevated CRP and/or MRI+) and mNY-negative by centrally-read baseline radiographs. Patients

had to have received at least 1 dose of study drug (PBO or CZP 200mg Q2W) during the double-blind period. Data from the dose-blind period (from AS001) and any open-label periods (from AS001 and AS0006) were excluded. Also, data from patients, who escaped in study AS001 and were re-randomized to CZP in a blinded manner, were excluded. In some analyses of rarer events, e.g., AESIs, UCB did provide an alternate Pool S1 analysis that included these patients in AS001 who escaped in a blinded manner. These patients' data were included within the PBO treatment group until the point of escape and then within the CZP group after escape through the end of the double-blind period.

The secondary safety pool (Pool S2) consisted of all patients treated with CZP in all studies which have included patients with nr-axSpA, as listed above. As with Pool S1, patients from AS001 were only included in Pool S2 if they met AS0006 eligibility criteria. For Pool S2 analyses, there are 3 groups summarized. The first group included all patients who were received CZP 200mg Q2W during the double-blind, placeb-controlled period; this group was the same as the CZP arm in Pool S1. The second group combined the safety data from all patients who received CZP 200mg Q2W from all studies (regardless of period or blinding). Lastly, the third group included safety data from all patients who received either dose of CZP (i.e., 200mg Q2W or 400mg Q4W) in all studies.

Table 50 shows the number of patients in each safety pool by study. In Pool S1, the numbers of patients in the PBO and CZP groups are comparable within each study. Patients from AS0006 represent the majority. Pool S2 is represented mostly by patients from studies AS0006 and AS0005.

Table 50. Number of Patients Within Each Safety Pool by Study

	Pool S1		Pool S2		
Study Number	PBO	CZP 200mg Q2W	CZP 200mg Q2W in PC studies	CZP 200mg Q2W in all studies	CZP (200mg Q2W and 400mg Q4W) in all studies
AS0006	157	159	159	303	303
AS001	30	23	23	38	72
AS0005	N/A	N/A	0	327	327
AS0007	N/A	N/A	0	12	12
Total	187	182	182	680	714

PBO column in Pool S1 includes all patients randomized to PBO along with status for first 24 weeks of study AS001 or for first 52 weeks of study AS0006.
All CZP 200mg Q2W column in Pool S2 includes CZP 200mg Q2W column as well as patients in PBO escaping to CZP.
Of the 158 patients in the PBO group in AS0006, only 157 met OSI criteria and were included in analyses.
Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks
[Source: UCB, Summary of Clinical Safety, Table 1-3. Dated Sep 24, 2018: page 20.]

Table 51 presents the extent of exposure through Week 52 for Pools S1 and S2. UCB defined exposure utilizing a "narrow sense" and a "broad sense." With the narrow approach, exposure was calculated as follows:

- For patients on CZP 400mg Q4W, date of last administration of CZP – date of first administration of CZP + 28 days.
- For patients on CZP 200mg Q2W, date of last administration of CZP – date of first administration of CZP + 14 days.
- For patients on PBO, date of last administration of PBO – date of first administration of PBO + 14 days.

With broad approach, 5 half-lives of CZP were taken into account. Therefore, patients were regarded to be exposed to CZP from first injection to last injection + 70 days.

Table 51. Extent of Exposure for Safety Pools (S1 and S2)

	Pool S1		Pool S2	
	PBO N=187	CZP 200mg Q2W N=182	All CZP 200mg Q2W in all studies N=680	All CZP (200mg Q2W and 400mg Q4W) in all studies N=714
Duration of exposure in **narrow sense** (weeks)				
Mean (SD)	28.0 (16.4)	42.7 (14.6)	56.4 (34.4)	59.7 (40.5)
Median	20.0	51.9	48.0	48.0
Minimum, maximum	2, 54	2, 55	1, 204	1, 204
Total study medication duration (sum of patient-years)	100.3	148.9	735.0	817.3
Duration of exposure in **broad sense** (weeks)				
Mean (SD)	29.1 (17.5)	44.4 (15.3)	59.2 (35.3)	62.6 (41.5)
Median	20.0	52.0	52.9	54.2
Minimum, maximum	4, 68	0, 68	0, 212	0, 212
Total study medication duration (sum of patient-years)	104.2	154.9	770.9	856.6

Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks; SD=standard deviation
[Source: UCB, Summary of Clinical Safety, Table 1-5. Dated Sep 24, 2018: page 41-42.]

Using the narrow definition of exposure, patients received treatment for a mean of 28.0 weeks in the PBO arm and 42.7 weeks in the CZP arm in Pool S1. In Pool S2, patients in the All CZP 200mg Q2W in All Studies column received treatment for a mean of 56.4 weeks, whereas patients in the All CZP in All Studies column received treatment for a mean of 59.6 weeks. UCB noted that, in Pool 1, most patients (64.8%) in the CZP arm received between 12 to 18 months of treatment, and most patients (51.9%) in the PBO arm received 3 to 6 months of treatment. The majority of patients in both All CZP 200mg Q2W and All CZP (57.5% and 55.3%, respectively) were exposed for 6 to 12 months.

Adequacy of the safety database:

In Section 8.1.2 and 8.1.4, the baseline demographics and baseline disease activity of the patient population are describes. These patients would represent those in the primary safety pool (Pool S1). In general, these patients appear to adequately represent what is known regarding the broad population of patients with nr-axSpA. It is notable that the large majority of enrolled patients is white, and this appears to be consistent with the axSpA population although the diagnosis of nr-axSpA is newly characterized.

Baseline measures of inflammation were comparable across arms in each safety pool. Most patients in Pools S1 and S2 were MRI+ (in Pool S1, 72.2% in the PBO arm and 72.0% in the CZP arm; in Pool S2, 79.6% in the All CZP 200mg Q2W arm and 78.2% in the All CZP arm). However, in terms of CRP, slightly more patients had an elevated CRP in Pool S1 (55.6% in PBO arm and 56.0% in CZP arm), whereas slightly more patients had a normal CRP in Pool S2 (elevated CRP noted in 44.3% in All CZP 200mg Q2W arm and 45.8% in All CZP arm). Table 52 shows the baseline categories of inflammation, MRI+/CRP+, MRI+/CRP-, MRI-/CRP+. All categories were represented in both study pools with more patients being MRI+/CRP-.

Table 52. Baseline MRI/CRP Category in Safety Pools

	Pool S1		Pool S2	
	PBO N=187	CZP 200mg Q2W N=182	All CZP 200mg Q2W in all studies N=680	All CZP (200mg Q2W and 400mg Q4W) in all studies N=714
Baseline Objective Inflammation Category, n (%)				
MRI+/CRP+	52 (27.8)	53 (29.1)	179 (26.3)	188 (26.3)
MRI+/CRP-	83 (44.4)	78 (42.9)	362 (53.2)	370 (51.8)
MRI-/CRP+	52 (27.8)	49 (26.9)	122 (17.9)	139 (19.5)
MRI-/CRP-	0	2 (1.1)	17 (2.5)	17 (2.4)

Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks; MRI=magnetic resonace imaging; CRP=C-reactive protein
[Source: UCB, Summary of Clinical Safety, Table 1-10. Dated Sep 24, 2018: page 49-50.]

CZP is already marketed for other indications at the doses studied for nr-axSpA. In addition, it is approved for AS, which is another diagnosis on the spectrum of axSpA. In the primary safety pool (Pool S1), 118 patients were exposed to >12 months of CZP, and, in Pool S2, 253 patients were exposed to >12 months of CZP. Thus, with these considerations, the size and adequacy of the safety database for CZP in nr-axSpA is adequate.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Other than the issues already discussed under the review of efficacy (Section 8.1.2), there are no important issues regarding data quality or quality of the overall submission that had an effect on the safety review.

Categorization of Adverse Events

UCB utilized standard definitions for adverse events (AEs) and serious adverse events (SAEs). A treatment-emergent adverse event (TEAE) was defined as an AE that occurred after first study drug administration until last study drug administration + 70 days. UCB's definition of TEAE was appropriate.

Adverse events were analyzed based on the Medical Dictionalry of Regulatory Activities (MedDRA) version 19.0 coded terms. UCB recoded AEs from study AS001 with version 19.0 terms so that all events could be tabulated using a single common dictionary version. All medications were coded or recoded using the World Health Organization Drug Dictionary version Sep 2015.

UCB determined the adverse events of special interest (AESIs) based on the known safety of TNF inhibitors. UCB utilized different queries in order to identify and summarize the AESIs, and these queries and definitions are described under each AESI in Section 8.2.5.

Routine Clinical Tests

The schedule of assessments (outlined in the tables in Section 15.3) specify the laboratory tests and the time points that they were conducted. In general, the safety assessment methods and time points were reasonable and adequate for nr-axSpA and for CZP (a TNF inhibitor that is already marketed for other indications).

Laboratory toxicity grades were determined by the Rheumatology Common Toxicity Criteria (RCTC) version 2.0. The Applicant considered a markedly abnormal laboratory value as one that was a Grade 3 or higher toxicity, as listed below.

- Hgb < lower limit of normal (LLN) and decrease from baseline >2 g/dL
- Hgb < 8 g/dL
- WBC < 2000/µL
- Lymphocyte count < 500/µL
- Neutrophil count < 1000/µL
- Platelet count < 50,000/µL
- ALT > 3x upper limit of normal (ULN)
- AST > 3x ULN
- Alkaline phosphatase (ALP) > 3x ULN
- Creatinine > 1.8x ULN
- Calcium > 12.5 mg/dL
- Calcium < 7 mg/dL
- Creatine kinase (CK) > 4x ULN
- Glucose > 250 mg/dL
- Glucose < 40 mg/dL
- Potassium > 6.4 mmol/L
- Potassium < 3 mmol/L
- Sodium < 125 mmol/L

- Bilirubin ≥ 2x ULN
- Uric acid ≥ 3x ULN

8.2.4. Safety Results

Table 53 summarizes the overall safety for both safety pools. In Pool S1, more patients on CZP (n=140, 76.9%) experienced AEs compared to patients on PBO (n=121, 64.7%). When accounting for duration of exposure, the incidence rate of AEs was similar between treatment arms. In Pool S1, the incidence rate of AEs was 346.45 per 100 patient-years for the CZP arm and 384.62 per 100 patient-years for the PBO arm. In Pool S2, the incidence rates of AEs on CZP were lower at 257.07 per 100 patient-years in the All CZP 200mg arm and 268.49 per 100 patient-years in the All CZP arm.

Table 53. Summary of Safety in the Safety Pools for nr-axSpA (Pool S1 and S2), Week 0-52

	Pool S1				Pool S2			
	PBO N=187 100 pt-yrs=1.04		CZP 200mg Q2W N=182 100 pt-yrs=1.55		All CZP 200mg Q2W in all studies N=680 100 pt-yrs=7.71		All CZP (200mg Q2W and 400mg Q4W) in all studies N=714 100 pt-yrs=8.57	
	n (%)	#	n (%)	#	n (%)	#	n (%)	#
Any TEAE	121 (64.7)	400	140 (76.9)	537	474 (69.7)	1982	506 (70.9)	2301
Serious TEAEs	5 (2.7)	5	8 (4.4)	9	49 (7.2)	68	54 (7.6)	75
Patient discontinuations due to TEAEs	4 (2.1)	4	3 (1.6)	4	25 (3.7)	32	33 (4.6)	40
Permanent withdrawal of study medication due to AEs	4 (2.1)	4	3 (1.6)	4	27 (4.0)	35	36 (5.0)	45
Deaths	0	0	0	0	0	0	0	0

Events were censored for PBO patients who escaped to CZP.
Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks; pt-yrs=patient-years; TEAE=treatment-emergent adverse events; SAEs=serious TEAEs;
n=number of patients who experienced at least 1 TEAE in the category; #=number of individual occurrences of the TEAE in that category
[Source: UCB, Summary of Clinical Safety, Table 1-10. Dated Sep 24, 2018: page 49-50.]

SAEs, AEs leading to discontinuation, and deaths are reviewed in more detail in the sections below. It is notable that the overall number of these AEs were low. Thus, it will be difficult to make any conclusions from these data.

Table 54 presents just the double-blind period of the primary study to support this supplement, study AS0006. The overall summary of safety is very similar to Pool S1. Given the similarity

between the safety in DB period of AS0006 to Pool S1, the safety of AS0006 will not be presented separately for the rest of the review.

Table 54. Summary of Safety in Study AS0006 (DB Period)

	DB Period	
	PBO N=158 Sum of pt-yrs=94.01 n (%)	CZP 200mg Q2W N=159 Sum of pt-yrs=145.12 n (%)
Any TEAE	101 (63.9)	120 (75.5)
Serious TEAEs	3 (1.9)	8 (5.0)
Patient discontinuations due to TEAEs	3 (1.9)	3 (1.9)
Permanent withdrawal of study medication due to AEs	3 (1.9)	3 (1.9)
Deaths	0	0

Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks; Pt-ys=patient-years; TEAE=treatment-emergent adverse events; SAEs=serious TEAEs; n=number of patients who experienced at least 1 TEAE in the category; #=number of individual occurrences of the TEAE in that category
[Source: UCB, AS0006 Interim CSR, Table 11-2. Dated Sep 24, 2018: page 240.]

Deaths

No deaths occurred in any of the nr-axSpA studies through the data cutoff dates.

Serious Adverse Events

Table 53 shows that mores patients on CZP experienced an SAE in Pool S1 (n=5 [2.7%] on PBO and n=8 [4.4%]. No SAEs occurred in more than 1 patient in either treatment arm. The SAEs that occurred in the CZP arm included glaucoma, diarrhea, neuroborreliosis, malignant melanoma, ruptured ovarian cyst, ovarian enlargement, pharyngeal edema, tooth extraction, and deep vein thrombosis (DVT).

Taking into account duration of exposure, the incidence rates of overall SAEs were calculated for both safety pools. In Pool S1, the incidence rates were similar between the PBO and CZP arms, 4.91 per 100 patient-years and 5.25 per 100 patient-years respectively. In Pool S2, the incidence rates were only slightly higher than that for Pool S1, 6.61 per 100 patient-years for the All CZP 200mg Q2W group and 6.50 per 100 patient-years for the All CZP group. Few SAEs occurred in more than 1 patient in Pool S2. These included cholelithiasis (n=2 [0.3%] in the All CZP group), pneumonia (n=3 [0.4%] in the All CZP group), major depression (n=2 [0.3%] in the All CZP group), and COPD (n=2 [0.3%] in the All CZP group).

Serious infections are described separately in Section 8.2.5.1.

Dropouts and/or Discontinuations Due to Adverse Effects

Table 53 also summarizes the number of patients who discontinued treatment due to AEs in both safety pools. Focusing on Pool S1, the number of patients who discontinued treatment due to AEs was low and similar between PBO (n=4, 2.1%) and CZP 200mg Q2W (n=3, 1.6%). No AEs that led to discontinued occurred in more than 1 patient in either arm. In the CZP arm, the AEs leading to discontinued included hepatic function abnormal, neuroborreliosis, groin pain, and ovarian enlargement.

Incidence rates were calculated by taking into account duration of exposure. In Pool S1, the incidence rates of AEs leading to discontinuation were slightly higher in the PBO arm (3.87 per 100 patient-years) compared to the CZP 200mg Q2W arm (1.94 per 100 patient-years). In Pool S2, the incidence rates of the CZP arms were higher than that in Pool S1 but were low, 3.52 per 100 patient-years in the All CZP 200mg Q2W arm and 4.23 in the All CZP arm. Only 3 AEs occurred in more than 1 patient: drug hypersensitivity (n=2 [0.3%] in the All CZP arm), psoriasis (n=2 [0.3%] in the All CZP arm), and tuberculin test positive (n=3 [0.4%] in the all CZP arm).

Common Adverse Events

In Pool S1, the most common SOCs were Infections and infestations (32.6% in the PBO arm and 51.6% in the CZP arm), Musculoskeletal and connective tissue disorders (24.1% in the PBO arm and 20.3% in the CZP arm), and Gastrointestinal disorders (10.2% in the PBO arm and 20.3% in the CZP arm). The following PTs occurred in >5% of patients through the DB period, listed in descending order for the patients on CZP:

- Upper respiratory tract infection (8.6% in the PBO arm vs. 16.5% in the CZP arm)
- Nasopharyngitis (7.5% in the PBO arm vs. 13.2% in the CZP arm)
- Headache (4.3% in the PBO arm vs. 7.1% in the CZP arm)
- Axial spondyloarthritis (7.5% in the PBO arm vs. 6.0% in the CZP arm)
- Arthralgia (6.4% in the PBO arm vs. 5.5% in the CZP arm)

Laboratory Findings

Hematology
In evaluating the shifts from baseline, there were no obvious patterns in Pool S1. More patients on CZP compared to those on PBO shifted from normal at baseline to low post-baseline for parameters of leukocytes and neutrophils (leukocytes: 13.7% on CZP and 8.6% on PBO; neutrophils: 9.9% on CZP and 0.5% on PBO). Other white blood cells (lymphocytes and monocytes) did not show a similar shift.

Using the parameters for markedly abnormal values (i.e., Grade 3 or greater on the toxicity scale, described in Section 8.2.3), in Pool S1, there were no markedly abnormal values for platelets, leukocytes, or neutropils. Both treatment arms had markedly low hemoglobin (n=6 [3.2%] on PBO, n=3 [1.7%] on CZP). One patient on PBO had markedly low lymphocytes.

Lastly, in reviewing the AEs related to hematology values, most events occurred in the PBO arm (n=7) compared to the CZP arm (n=4). Anemia was reported in the CZP arm (n=2 [1.1%]) but was reported in more patients on PBO (n=4 [2.1%]). The other PT in the CZP arm was eosinophila (n=2 [1.1%]) with none reported on PBO.

Thus, based on the low number of events and lack of consistent findings, it was difficult to make conclusions regarding the risk on hematology parameters.

Chemistry
In evaluating shift from baseline, more patients on CZP shifted from normal at baseline to high post-baseline for CK (19.8% on CZP and 14.4% on PBO) and ALT (22.5% on CZP and 17.6% on PBO). On the other hand, more patients shift from normal to high for CRP in the PBO group (18.6% on PBO and 9.9% on CZP).

Markedly abnormal chemistry values were also evaluated. In Pool S1, none occurred for the parameters of potassium, sodium, creatinine, or bilirubin.

- Calcium abnormally low: n=1 (0.6%) on CZP vs. n=0 on PBO
- CK abnormally high: n=4 (2.2%) on CZP vs. n=3 (1.6%) on PBO
- ALT abnormally high: n=7 (3.9%) on CZP vs. n=2 (1.1%) on PBO
- ALP abnormally high: n=1 (0.6%) on CZP vs. n=0 on PBO
- Glucose abnormally high: n=1 (0.6%) on CZP vs. n=2 (1.1%) on PBO

UCB noted similar trends for CK and liver enzymes in Pool S2. However, the Applicant reported that the liver enzyme abnormalities were typically transient. Non-transient values often occurred in patients with potential contributing medical histories or concomitant medications. UCB also reported no associated AEs with the elevations in CK.

Table 55 presents the AEs associated with chemistry values in Pool S1. Overall numbers are low, and many events occurred as single events. There did appear to slightly more patients on CZP who experienced AEs related to elevations in liver enzymes (ALT increased, AST increased, Transaminases increased, and ALP increased). Additionally more patients on CZP (n=9, 4.9%) reported an elevated CK compared to PBO (n=5, 2.7%).

Table 55. Summary of AEs Related to Chemistry Values (Pool S1)

	Pool S1	
	PBO N=187 n (%)	CZP 200mg Q2W N=182 n (%)
Lipoprotein(a) increased	0	1 (0.5)
ALT increased	3 (1.6)	6 (3.3)
AST increased	1 (0.5)	2 (1.1)
Transaminases increased	0	1 (0.5)
LFT increased	1 (0.5)	1 (0.5)
Serum ferritin decreased	0	1 (0.5)
Blood CK increased	5 (2.7)	9 (4.9)
Blood ALP increased	0	1 (0.5)
Type 2 diabetes mellitus	0	1 (0.5)
Hypercholesterolemia	2 (1.1)	2 (1.1)
Hyperglycemia	1 (0.5)	0
Hyperlipidemia	1 (0.5)	0
Dyslipidemia	1 (0.5)	1 (0.5)
Hypokalemia	0	1 (0.5)

Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks; AE=adverse events; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CK=creatine kinase; LFT=liver function test; ALP=alkaline phosphatase
[Source: UCB, Summary of Clinical Safety, Table 3-4. Dated Sep 24, 2018: page 92-93.]

UCB evaluated post-baseline liver-associated enzymes separately. In Pool S1, generally more patients on CZP had an elevation in liver-associated enzymes.

- ALP ≥ 1.5x ULN: n=3 (1.7%) on CZP vs. n=2 (1.1%) on PBO
- ALT
  - ≥ 2x ULN: n=16 (8.9%) on CZP vs. n=6 (3.2%) on PBO
  - ≥ 3x ULN: n=7 (3.9%) on CZP vs. n=2 (1.1%) on PBO
- AST ≥ 2x ULN: n=2 (1.1%) on CZP vs. n=2 (1.1%) on PBO
- TB
  - ≥ 1x ULN: n=17 (9.4%) on CZP vs. n=10 (5.3%) on PBO
  - ≥ 1.5 x ULN: n=2 (1.1%) on CZP vs. n=3 (1.6%) on PBO

No patients in Pool S1 in any treatment arm met criteria fro Hy's law (i.e., TB ≥ 2x ULN *and* ALT or AST ≥ 3x ULN at the same visit). Similarly, no patients in Pool S2 met Hy's law.

In conclusion, in terms of abnormal chemistry values, the overall numbers are low. However, there did appear to be more patients on CZP who developed an elevation in liver enzymes and an elevation in CK. These elevations, however, did not appear to be clinically significant.

Vital Signs

Vital signs were not summarized for the safety pools.

In study AS0006, no clinically meaningful changes from baseline in vital signs measurements were noted. During the double-blind period, the most common abnormal vital sign measurement was a low systolic blood pressure (≤90mmHg and decrease of ≥20mmHg), which occurred in more patients on CZP (n=6) compared to PBO (n=4). In terms of AEs related to vital signs, during the doubl-bline period, 1 patient on CZP had a PT of increased blood pressure, and 1 patient on PBO had a PT of increased body temperature.

Immunogenicity

See the clinical pharmacy review in Section 6 for details regarding anti-drug antibody (ADA).

The majority of patients (97.3%) in study AS0006 developed anti-drug antibodies. UCB attempted to evaluate whether there were more AEs after ADA development, and it appeared that more patients did experience AEs after becoming ADA positive (64.0%) compared to before becoming ADA positive (39.9%). However, given that most patients became ADA positive by Week 12, the observation period was much longer for patients after becoming ADA positive. In fact, the Applicant noted that exposure-adjusted event rates were higher for patients prior to becoming ADA positive compared to after becoming ADA positive. In general, given the high number of patients with ADA, no conclusions can be made about ADA positivity and hypersensitivity reactions, AEs, or overall safety in study AS0006.

In study AS001, much fewer patients (9.6%) became ADA positive, and, thus, no meaningful conclusions on safety could be made because of the low numbers.

8.2.5. Analysis of Submission-Specific Safety Issues

The AEs of special interest (AESIs) for this submission included the known safety concerns with CZP and TNF inhibitors in general. These included serious infections (including opportunistic infections), malignancies (including lymphoma), serious cardiovascular events, congestive heart failure, demyelinating-like disorders, cytopenias (including aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leukopenia), serious bleeding events, lupus and lupus-like illness, and serious skin reactions (including Stevens Johnson Syndrome [SJS], toxic epidermal necrosis [TEN], and erythema multiforme). Although not considered AEs of special interest, UCB also summarized hepatic events, hypersensitivity reactions/anaphylactic reactions, injection site reactions, and psoriasis/psoriatic conditions. Each AESI is described in detail under the following subheadings.

8.2.5.1. Serious Infections

The serious infections were defined as the PTs that fell under the Infections and infestations SOC in the overall SAE table. Additionally, the Applicant identified opportunistic infections, including TB, by using UCB-defined search criteria and manual review by the project physician.

In Pool S1, 1 patient in the CZP 200mg Q2W arm had a serious infection of neuroborreliosis. No patients had an opportunistic infection.

In Pool S2, 11 (1.6%) patients in the All CZP 200mg Q2W arm and 13 patients (1.8%) in the All CZP arm had serious infections. Accounting for duration of exposure, the incidence rates were low and similar for both arms, 1.44 per 100 patient-years and 1.54 per 100 patient-years, respectively. Pneumonia (n=3 on CZP 200mg Q2W) and TB (n=2 on CZP 200mg Q2W) were the serious infections that occurred in more than 1 patient. The other serious infections occurred as single events and included cellulitis, encephalitis, legionella pneumonia, rotavirus gastroenteritis, infected dermal cyst, subcutaneous abscess, pulmonary tuberculosis (TB), TB, acute sinusitis, and peritonsillar abscess.

UCB considered 3 of these serious infections in Pool S2 to be opportunistic: the 2 cases of TB (both in patients in study AS0006 who switched from PBO to OL CZP 200 mg Q2W) and the legionella pneumonia. In addition, there was with a nonserious infection, esophageal candidiasis, which occurred in a patient on 400 mg Q4W.

8.2.5.2. Malignancies

The Applicant utilized the standard MedDRA queries (SMQs), “Malignant or unspecified tumours” and “Malignant tumors,” to determine the number of malignancies that occurred. UCB then summarized malignancies that included or excluded non-melanotic skin cancers.

In Pool S1, 1 patient (0.5%) in the PBO group developed a malignant melanoma stage I. Two patients (1.1%) in the CZP 200mg Q2W arm were diagnosed with malignant melanoma and basal cell carcinoma.

In Pool S2, the numbers of patients with malignances remained low. The incidence rates were very low at 0.26 and 0.35 per 100 patient-years in the All CZP 200mg Q2W arm and All CZP arms, respectively. In addition to the 2 patients with malignancies already accounted for in Pool S1, Pool S2 also captured 1 patient in the All CZP arm who developed malignant astrocytoma.

8.2.5.3. Cardiovascular events

The Applicant determined the number of serious cardiovascular events by searching the SAEs with the SMQs of "Haemorrhagic central nervous system vascular conditions" and "Ischemic central nervous system vascular conditions." Additionally, serious cardiovascular events were SAEs that fell under the following High Level Terms (HLTs): "Ischaemic coronary artery disorders" except for the PTs of "chest pain" or "chest discomfort," "Heart failures NEC," "Left ventricular failures," or "Right ventricular failures."

Based on these search criteria, there were no serious cardiovascular events in Pool S1 or S2.

8.2.5.4. Congestive Heart Failure (CHF)

Any AEs that coded to the PT "cardiac failure congestive" were included under the AESI of CHF. There were no cases of CHF in either safety pool.

8.2.5.5. Demyelinating-like disorders

The Applicant utilized the SMQ of "Demyelination" to capture all the AESIs of demyelinating-like disorders.

In Pool S1, there were no demyelinating-like disorders. In Pool S2, 1 patient on CZP 200 mg Q2W developed optic neuritis.

8.2.5.6. Cytopenias

The SMQ "Haematopoietic cytopenia" to query SAEs was used to identify AESIs of pancytopenia, aplastic anemia, thrombocytopenia, neutropenia, and leukopenia. Based on this search criteria, no patients developed cytopenias in Pool S1 or S2.

8.2.5.7. Serious bleeding events

For the AESI of serious bleeding events, UCB utilized the SMQ "Haemorrhage terms (excl laboratory terms)" in SAEs. Based on this search criteria, there were no patients with serious bleeding events in either safety pool.

8.2.5.8. Lupus and lupus-like syndromes

Projects physicians manually identified lupus and lupus-like illness, and none were reported for both safety pools.

8.2.5.9. Serious skin reactions

Project physicians manually identified serious skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme. No serious skin reactions were noted in the safety pools.

8.2.5.10. Hepatic events

UCB identified hepatic events by utilizing SMQs for "cholestasis and jaundice of hepatic origin," "hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions," "hepatitis, noninfectious," "liver-related investigations, signs and symptoms," and "liver-related coagulation and bleeding disturbances."

In Pool S1, 5 patients (2.7%) in the PBO arm and 10 patients (5.5%) in the CZP 200 mg Q2W arm had hepatic events. Increased ALT (n=3 in the PBO group and n=6 in the CZP group) and increased AST (n=1 in the PBO group and n=2 in the CZP group) were the hepatic events that occurred in more than 1 patient. The other hepatic events in the CZP arm were single events but actually have been similar types of events. These events included liver disorder, hepatic function abnormal, hypertransaminases, hepatic steatosis, toxic hepatitis, and increased transaminases.

The incidence rates in Pool S1 were 4.88 per 100 patient-years in the PBO arm and 6.72 per 100 patient-years in the CZP arm. In Pool S2, the incidence rates were lower than the CZP arm in Pool S1. The incidence rate was 4.70 per 100 patient-years in the All CZP 200 mg Q2W arm and 4.61 per 100 patient-years in the All CZP arm, accounting for 35 patients and 38 patients, respectively. The most common PT to define hepatic events in Pool S2 was also increased ALT and increased AST.

Additionally, see discussion regarding liver-associated enzymes in Section 8.2.4 under "Laboratory Findings." As noted in Section 8.2.4, there were no Hy's law cases in either safety pool.

8.2.5.11. Hypersensitivity and anaphylactic reactions

UCB considered the following PTs that occurred within 1 day of study medication injection to be hypersensitivity reactions: 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, and type IV hypersensitivity reaction.

UCB defined anaphylactic reactions in three ways. First, AEs that fell under the PTs in Category A were all considered anaphylactic reactions. Anaphylactic reactions were also defined by any

AE coded as a PT in Category B and an AE coded as a PT in Category C that started on the same date. The last definition of anaphylactic reactions was any AE coded as a PT in Category D and an AE coded as a PT in Category B or C that started on the same date. The PTs under Categories A, B, C, and D are listed below.

- Category A were PTs that were part of the SMQ "Anaphylactic reaction": anaphylactic reaction, anaphylactic shock, anaphylactic transfucion reaction, anaphylactoid reaction, anaphylactoid shock, circulatory collapse, dialysis membrane reaction, Kounis syndrome, shock, shock symptom, and type I hypersensitivity.
- Category B included the following PTs: acute respiratory failure, asthma, bronchial oedma, bronchospasm, cardiorespiratory distress, chest discomfort, choking, choking sensation, circumoral oedema, cough, cyanosis, dyspnoea, hyperventilation, irregular breathing, laryngeal dyspnea, laryngea oedema, laryngospasm, lyngotracheal oedema, mouth swelling, nasal obstruction, oedema mouth, oropharyngeal spasm, oropharyngeal swelling, respiratory arrest, respiratory distress, respiratory dyskinesia, respiratory failure, reversible airways obstruction, sensation of foreign body, sneezing, stridor, swollen tongue, tachypnoea, throat tightness, tongue oedema, tracheal obstruction, tracheal oedema, upper airway obstruction, and wheezing.
- Category C consisted of the following PTs: allergic oedema, angioedema, erythema, eye oedema, eye pruritus, eye swelling, eyelid oedema, face oedema, flushing, generalized erythema, injection site urticarial, lip oedema, lip swelling, nodular rash, ocular hyperaemia, oedema, periorbital oedema, pruritus, pruritus allergic, pruritus generalized, rash, rash generalized, rash pruritic, skin swelling, swelling, swelling face, uricaria, and uricaria popular.
- Lastly, Category D includind the following PTs: blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, cardiac arrest, cardiorespiratory arrest, cardiovascular insufficiency, diastolic hypotension, and hypotension.

Utilizing these different search criteria and categories, 1 patient on PBO in Pool S1 developed a drug hypersensitivity reaction, but it was a reaction to azithromycin. In Pool S2, there were 4 additional patients on CZP 200mg Q2W who had an AE of drug hypersensitivity. The Applicant noted no events consistent with anaphylaxis by any definition in either safety pool.

8.2.5.12. Injection site reactions

The PTs that fell under the High Level Term (HLT) "injection site reactions" were also evaluated by the Applicant. In Pool S1, more patients on the CZP arm (n=9, 4.9%) had injection site reactions compared to patients on the PBO arm (n=2, 1.1%). In the CZP arm, patients experienced injection site pain (n=2), injection site bruising (n=3), injection site reaction (n=3), and injection site erythema (n=1); whereas, in the PBO arm, patients just experienced injection site pain (n=1) and injection site erythema (n=2). The exposure-adjusted incidence rate was lower in the PBO arm (1.94 per 100 patient-years) than in the CZP arm (6.03 per 100 patient-

years). The incidence rate was lower in Pool S2 with 4.92 events per 100 patient-years in the All CZP 200mg Q2W arm and 4.81 events per 100 patient-years in the All CZP arm.

8.2.5.13. Psoriasis (PSO)

Psoriasis is a known/expected AE of TNF inhibitors. In Pool S1, more patients (n=4, 2.2%) on CZP had an AE of PSO compared to patients on PBO (n=2, 1.1%). In Pool S2, there were additional events of pustular PSO (n=2 on CZP 200 mg Q2W), dermatitis psoriasiform (n=1 on CZP 400 mg Q4W), and guttate PSO (n=2 pm CZP 200 mg Q2W).

8.2.6. Safety Analyses by Demographic Subgroups

UCB conducted multiple safety analyses by various demographic subgroups, including age, gender, race, BMI category, region, and NSAID use at baseline. In general, these analyses were consistent with the safety analyses of the overall safety population.
As shown in Table 56, there appeared to be slightly more AEs in females as compared to males in Pool S1, particularly in terms of SAEs and AEs leading to discontinuation. However, amongst females, the number of patients with SAEs and AEs leading to discontinuation was similar between the PBO and CZP arms. Thus, there did not appear to be an increased risk of AEs from CZP.

Table 56. Summary of Safety in Pool S1 (Wk 0-52, Male vs. Female)

	Males		Females	
	PBO N=88 n (%)	CZP 200mg Q2W N=87 n (%)	PBO N=99 n (%)	CZP 200mg Q2W N=95 n (%)
Any TEAE	53 (60.2)	64 (73.6)	68 (68.7)	76 (80.0)
Serious TEAEs	1 (1.1)	4 (4.6)	4 (4.0)	4 (4.2)
Patient discontinuations due to TEAEs	0	0	4 (4.0)	3 (3.2)
Permanent withdrawal of study medication due to AEs	0	0	4 (4.0)	3 (3.2)
Deaths	0	0	0	0

Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks; TEAE=treatment-emergent adverse events; SAEs=serious TEAEs; n=number of patients who experienced at least 1 TEAE in the category
[Source: UCB, Summary of Clinical Safety Tables, Table 5.2.2.2. Dated Sep 24, 2018: page 602-603.]

8.2.7. Specific Safety Studies/Clinical Trials

Study AS001 makes up part of the pooled safety data that are assessed above. However, the primary safety pool (Pool S1) included patients from AS001 who received CZP 200mg Q2W. In order to compare the safety of the 400mg Q4W dose, the safety of the nr-axSpA population

(based on centrally-read baseline radiographs) who received both doses of maintenance CZP during the PBO-controlled period in study AS001 is evaluated. Table 57 shows the summary of safety in study AS001.

Table 57. Summary of Safety in the nr-axSpA Population† in Study AS001 (24-wk DB period)

	PBO[a] N=35 n (%)	CZP 200mg Q2W N=33 n (%)	CZP 400mg Q4W N=30 n (%)
Any TEAEs	21 (60.0)	27 (81.8)	25 (83.3)
Serious Adverse Events	1 (2.9)	1 (3.0)	3 (10.0)
Discontinuation due to TEAEs	1 (2.9)	0	3 (10.0)
Deaths	0	0	0

†Patients are classified as nr-axSpA based on centrally read baseline radiographs
a: PBO arm does not include AEs in patients who escaped to CZP
Abbreviations: PBO=placebo; CZP=certolizumab pegol; Q2W=every two weeks; Q4W= every four weeks; TEAE=treatment-emergent adverse events; SAEs=serious TEAEs
[Source: UCB response to clinical IR: Ad Hoc Tables Response 2, Table 8.1.5. Dated May 17, 2013, page 144.]

The number of SAEs was low, and no PT was documented more than once. In the PBO arm, there was an AE of drug hypersensitivity. In the CZP 200mg Q2W arm, there was an AE of increased GGT. In the CZP 200mg Q2W arm, the SAEs were SVT, abdominal pain, and cholelithiasis. One additional SAEs occurred in a patient with nr-axSpA (by central reading) prior to Week 24 but was reported after the database lock. This SAE occurred in a patient on PBO who developed intermittent dactylitis third finger of the right hand.

Similarly, the AEs leading to discontinuation were low. In the PBO arm, there was one patient (2.9%) with the AE of hepatitis. In the CZP 400mg Q4W arm, there were 3 patients (10%) with AEs of cholelithiasis, increased CRP, and gynecomastia.

In summary, overall AEs were low in study AS001 in the nr-axSpA population, and it is difficult to make any general conclusions. However, there did not appear to be more safety concerns in the 400 mg Q4W dose compared to the 200 mg Q2W.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No data on human carcinogenicity or tumor development are included in this supplement.

Human Reproduction and Pregnancy

Two pregnancies occurred in the nr-axSpA population, safety Pool S2. One patient was taking CZP 200mg Q2W, and one patient received CZP 400mg Q2W. No other details are provided regarding these pregnancies.

Pediatrics and Assessment of Effects on Growth

Pediatric studies are waived for this indication. See Section 10 for more details regarding the waiver. At this time, CZP is not indicated for any pediatric populations.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

UCB reported no accidental or intentional overdoses with CZP in the nr-axSpA population. Drug abuse potential, withdrawal, and rebound were not evaluated in the clinical studies.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

UCB's last Periodic Safety Update Report (PSUR) analyzed the global postmarket experience with CZP through the database lock date of March 6, 2018. An estimated 13,463 patients have been exposed to CZP in completed and ongoing clinical studies. Exposure to CZP is estimated to be (b) (4) patient-years during the 1-year interval of the PSUR an (b) (4) patient-years cumulatively for the marketing experience across all indications, which includes nr-axSpA in certain countries. UCB reported no postmarket findings that could potentially alter the favorable benefit-risk profile of CZP for its approved indications.

Expectations on Safety in the Postmarket Setting

Based on the safety analyses in the nr-axSpA population, there are no new safety issues that cause concern when considering how the drug may be used in the postmarket setting. As discussed in Section 12 below, no new safety issues have been identified to warrant a need for additional risk management activities in the postmarket setting.

8.2.10. Integrated Assessment of Safety

Adverse events were few in the safety pools for CZP nr-axSpA program. More patients on CZP 200mg Q2W (n=14, 76.9%) experienced any AE compared to patients on PBO (n=121, 64.7%) in Pool S1, which covered the double-blind, placebo-controlled period of studies AS0006 and AS001. The most common AEs fell into the categories of Infections and infestations, Musculoskeletal and connective tissue disorders, and Gastrointestinal disorders; these were consistent with the known safety profile of CZP.

In reviewing SAEs, AEs leading to discontinuation, and AESIs, the overall numbers were low, and the rarity of these events makes it difficult to make definitive conclusions regarding safety of

CZP in nr-axSpA. In general, though, the data are adequate to conclude that the safety is no worse than the safety of CZP in other indications.

- No deaths were reported for either safety pool.

- Numerically more SAEs occurred in the CZP arm (n=8, 4.4%) compared to the PBO arm (n=5, 2.7%) in Pool S1. The SAEs that occurred in the CZP arm included glaucoma, diarrhea, neuroborreliosis, malignant melanoma, ruptured ovarian cyst, ovarian enlargement, pharyngeal edema, tooth extraction, and deep vein thrombosis (DVT).

- AEs leading to discontinuation were similar across both treatment arms, n=3 (1.6%) in the CZP group and n=4 (2.1%) in the PBO group. The reported AEs in the CZP arm included hepatic function abnormal, neuroborreliosis, groin pain, and ovarian enlargement.

- No associated pattern in hematologic abnormalities was noted. However, there did appear to be more patients on CZP who developed an elevation in liver enzymes and an elevation in CK. For example, 7 patients on CZP (3.9%) experienced an ALT ≥ 3x ULN, whereas 2 patients on PBO (1.1%) had the same elevation. No patients met Hy's law. In general, these elevations did not appear to be clinically significant.

- Very few AESIs occurred in the safety pools, particularly Pool S1.
    - In terms of serious infections, only 1 event (neuroborreliosis) occurred in a patient on CZP in Pool S1. In Pool S2, there were 13 patients on both doses of CZP who developed serious infections. The types of infections were consistent with what has been seen with CZP in other programs. Four opportunistic infections occurred in Pool S2, including 2 cases of TB, 1 case of legionella pneumonia, and 1 case of esophageal candidiasis (not serious).
    - Three malignancies occurred in Pool S2. All patients received CZP. The types of malignancies included malignant melanoma, basal cell carcinoma, and astrocytoma.
    - In Pool S2, 4 patients on CZP 200mg Q2W developed a hypersensitivity reaction. There were no cases of anaphylaxis in either safety pool.
    - More injection site reactions occurred in patients on CZP compared to patients on PBO. In Pool S1, 9 patients in the CZP arm (4.9%) had injection site reactions compared to 2 patients in the PBO arm (1.1%).

To evaluate the safety of the 400 mg Q2W dose, the overall safety in study AS001 was reviewed. More patients on CZP (81.8% on CZP 200mg Q2W and 83.3% on CZP 400mg Q4W) experienced AEs compared to patients on PBO (60.0%). However, the total number of AEs was similar between maintenance doses. The number of SAEs and AEs leading to discontinuation was very low for all treatment arms, and, thus, it is difficult to make any conclusions. There

were slightly more patients on CZP 400 mg Q4W (10%) who experienced SAEs compared to patients on CZP 200 mg Q2W (3.0%) and PBO (2.9%).

In conclusion, the safety data from CZP in the nr-axSpA studies are consistent with the known safety profile of TNF inhibitors and, specifically, of CZP for other indications. There were no new safety signals. The current labeling for the other approved indications will cover the findings from the nr-axSpA trials.

8.3. Statistical Issues

As AS0006 is the primary study to support approval for this indication, refer to Section 8.1.2 for details regarding the statistical issues that impacted the overall conclusion.

8.4. Conclusions and Recommendations

See Sections 8.1.6 (Integrated Assessment of Effectiveness) and 8.2.10 (Integrated Assessment of Safety) for details regarding the conclusions on efficacy and safety.

AS0006 was a 52-week, double-blind, placebo-controlled study to evaluate the efficacy and safety of CZP 200mg Q2W in 317 patients with nr-axSpA. It served as the primary support for efficacy in this resubmission of supplement 237. In addition, UCB re-submitted data from study AS001 as a supportive study to AS0006. AS001 was the originally-submitted 24-week, double-blind, placebo-controlled study to evaluate efficacy and safety of CZP 200 mg Q2W and CZP 400 mg Q4W in patients with active axSpA, including 98 patients with nr-axSpA (based on central read of baseline radiographs). Study AS0006 met its primary endpoint of ASDAS-MI at Week 52 as well as secondary endpoints, including ASAS40 at Week 52. A large proportion of patients, particularly in the PBO arm, switched therapy during the course of the study to OL CZP. Different analyses to account for this change in therapy, including assessment of all observed data and assessments at different time points, continued to support the benefit of CZP 200mg SC Q2W over PBO. The chronic dosing regimen of CZP 400 mg Q4W was not studied in AS0006. Instead, UCB relied on the data from AS001. The efficacy results for both doses of CZP from study AS001 supported the results from study AS0006 and supported the use of CZP 400 mg Q4W dosing regimen.

Safety was supported by data from study AS0006 and AS001, as well as ongoing studies AS0005 and AS0007. The overall number of safety events in the nr-axSpA program was low, and, thus, it was difficult to make any definitive conclusions regarding the safety of CZP in nr-axSpA. There were no new safety signals. The safety profile was essentially consistent with what is known regarding the safety of CZP for other indications.

The review team concludes that the overall benefit-risk is favorable to support the approval of CZP at 200 mg SC Q2W or 400 mg SC Q4W, preceded by a loading dose of 400mg SC initially and

Weeks 2 and 4, for the treatment of active non-radiographic axial spondyloarthritis with objective signs of inflammation.

APPEARS THIS WAY ON ORIGINAL

9 Advisory Committee Meeting and Other External Consultations

An advisory committee (AC) meeting was not recommended for this supplemental BLA. The first submission of this supplement was already discussed at an AC meeting on July 23, 2013. In this resubmission, the Applicant addressed all the Agency's issues and recommendations detailed in the Complete Response letter from the first submission.

APPEARS THIS WAY ON ORIGINAL

10 Pediatrics

UCB requested a full waiver of the requirements for a pediatric assessment in patients ages 0 to 17 because studies are impossible or highly impractical. AxSpA (which includes AS and nr-axSpA) is recognized by the Agency as an adult conditions that qualify for a waiver because they rarely occur in pediatrics.

Lastly, to support the request for a full waiver, UCB provided the following background information. Juvenile Idiopathic Arthritis (JIA) is an arthritis of unknown cause that begins in children (before the age of 16), and it is currently classified according to the International League of Association for Rheumatology (ILAR). There are 7 subtypes, and the pediatric equivalent indication for adult nr-axSpA falls under enthesitis-related arthritis (ERA). The US prevalence of overall JIA is 4.5 per 100,000 persons. Based on a review of literature, UCB estimates that the prevalence rate in pediatric patients with nr-axSpA is approximately 1.0 per 100,000 persons. This estimate is based on 2 assumptions: (1) ERA makes up 10% of all JIA diagnoses, and (2) approximately half of AxSpA patients have nr-axSpA. Thus, the number of potential pediatric patients with a pediatriac equivalent of nr-axSpA is very low.

UCB's request for waiver was discussed at the Pediatric Review Committee (PeRC) meeting on January 30, 2019, and was found to be acceptable.

APPEARS THIS WAY ON ORIGINAL

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Table 58 presents a high-level summary of the labeling proposal and subsequent interactions between the Applicant and the Agency. Most of the discussion involved the presentation of data from studies AS0006 and AS001 for nr-axSpA.

Table 58. Summary of Significant Labeling Changes (High Level Changes)

Section	Labeling Discussions
Highlights, 1.5 Indications and Usage	The proposed new indication in the USPI: *Treatment of adults with non-radiographic axial spondyloarthritis with objective signs of inflammation* On March 18, 2019, the Agency provided labeling revisions that included the addition of "active" prior to "nr-axSpA" in order to be consistent with other rheumatologic diagnoses in Section 1.
2.5 Dosage and Administration	The Agency agreed with the proposed dosing. *The recommended dose of CIMZIA for adult patients with non-radiographic axial spondyloarthritis 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.*
6.1 Clinical Trials Experience under ADVERSE REACTIONS	The Agency agreed with the proposed safety statement for nr-axSpA. *CIMZIA has been studied in 317 patients with non-radiographic axial spondylarothritis (nr-axSpA-1). The safety profile for patients with nr-axSpA treated with CIMZIA was similar to the safety profile seen in patients with RA and previous experience with CIMZIA.*
6.2 Immunogenicity under ADVERSE REACTIONS 12.3 Pharmacokinetics: Special Populations	The Applicant recommended adding information regarding a new assay to detect antidrug antibodies (ADA) that was used for the first time in nr-axSpA-1 study. However, the Agency noted that, in the new study, there were 97% ADA positive patients and only 3% ADA negative. Thus, with the limited data in the current study, it was difficult to draw conclusions about the impact of ADA on efficacy and to ascertain the impact of ADA on change in clearance (CL). This was conveyed to the Applicant in labeling revisions, dated March 5, 2019.

	In labeling revisions dated March 21, 2019, the Agency recommended that clarifying that test results from this new electrochemilunisence (ECL)-based bridging assay was highly dependent on the sensitivity and specificity of the assay.
14.5 Non-radiographic Axial Spondyloarthritis under CLINICAL STUDIES	The Applicant proposed the following presentation of efficacy data from AS0006 and AS001. The Applicant's originally proposed labeling are bolded and italicized. (b) (4) The Agency had concerns (b) (4) (b) (4) There was lack of consistent collection of efficacy assessments (i.e., schedule of assessments was less frequent) after switching therapy. Imputed data based on last observation carried forward are not appropriate. Also, all observed data collected after cross-over to OL CZP could be affected by differential continuation rates, patient expectations of treatments, knowledge of treatment received. Therefore, in labeling revisions dated March 5 and 18, 2019, the Agency recommended that the Applicant make the following changes. 1. Addition of language in the description of the study of nr-axSpA-1 (AS0006) to explain how patients could switch therapy at the discretion of the Investigator 2. Addition of components of ASAS response criteria. ASAS response was an important secondary endpoints and has more regulatory precendence for the indication of AS. 3. The components of ASDAS-MI and ASAS should only be reported until Week 12. 4. ASDAS-MI response over time should also only be reported through Week 12. (b) (4) The Agency did not agre (b) (4) (b) (4) and, thus, is not appropriate for inclusion in Section 14 of the USP (b) (4)

	(b) (4) (b) (4) The Agency advised that the Applicant remove these results in labeling revisions dated March 5 and 18, 2019. • (b) (4) As back pain and total spinal pain are to be included in the table of components of ASDAS-MI and ASAS, the presentation of the (b) (4) was felt to be redundant. The Agency advised the Applicant to remov (b) (4) (b) (4) n the labeling revisions dated March 5, 2019. • ***ASAS20 and ASAS40 at Week 12 from study AS001*** The Agency agreed with presenting ASAS20 and ASAS40 data from AS-1 (study AS001). In labeling revisions dated March 5, 2019, the Agency advised the Applicant to present the results from the population categorized as nr-axSpA based on central reading of the baseline radiographs. This approach would be more consistent with the population from study AS0006. Additionally, the Agency advised the Applicant to present the data for each dose (200 mg Q2W and 400 mg Q4W) separately to describe the clinical data supporting the dosing regiment that was studied only in Study AS001, i.e. 400 mg Q4W. • (b) (4) (b) (4) ***health-related outcome*** (b) (4) For the same reasons described above, the Agency did not agree (b) (4) Instead, the Applicant should summarize the data for Week 12. Also, the Applicant provided justification for the use of ASQoL in nr-axSpA but did not provide sufficient information t (b) (4) (b) (4) Therefore, in the labeling revisions dated March 5, 2019, the Agency advised the Applicant to remove (b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

No new risk management plans are submitted as part of this supplement. As no new safety signals have been identified, no new REMS are necessary.

13 Postmarketing Requirements and Commitment

As above, UCB will receive a full waiver for postmarketing studies required to achieve compliance with PREA.

There are no potential or new safety or efficacy issues determined from this review that warrant further assessment with a postmarketing requirement (PMR) or postmarketing commitment (PMC).

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14 Division Director(Clinical) /Designated Signatory Comments

UCB resubmitted supplement 237 to Biological Licensing Application (BLA) 125160 for certolizumab pegol to address the deficiencies listed in the Complete Response (CR) letter issued on October 17, 2013, and to support a new indication: Treatment of adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation. The proposed dose is certolizumab pegol 400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week (Q2W) or 400 mg every 4 weeks (Q4W). No changes to the currently marketed presentations are being proposed in this supplemental BLA (sBLA).

In support of this supplement the Applicant has provided data from a new clinical study, Study AS0006, a 52-week, double-blind, placebo-controlled study with 317 patients with nr-axSpA with positive signs of inflammation, including sacroiliitis by MRI, elevated CRP, or both. The primary endpoint for study AS0006 was ASDAS-MI response at Week 52. Forty seven percent of patients on certolizumab pegol 200 mg Q2W experienced a clinical response, compared to 7% of patients on placebo ($p<0.001$). At Week 52, 57% of patients on certolizumab pegol achieved ASAS40 response compared to 16% on placebo ($p<0.001$). Notwithstanding the statistical considerations discussed in the statistical review, this study provides the primary evidence for the effectiveness of certolizumab pegol for the treatment of nr-axSpA. As further supportive evidence of effectiveness and to support the alternative dosing regimen, 400 mg Q4W, which was not studied in study AS0006, UCB included data from study AS001, a 24-week, double-blind, placebo-controlled study with 98 patients with nr-axSpA (based on central radiographic read). AS001 was the original study submitted for this proposed indication. Reviewed and considered together, both studies meet the evidentiary standard for effectiveness of certolizumab pegol in the proposed indication and support the proposed dosing regimens. The overall safety in nr-axSpA population was consistent with the known safety profile of certolizumab pegol.

The current submission has adequately addressed the October 17, 2013, CR letter deficiencies, including study duration and adequate measures of inflammation at baseline to ensure the selection of patients for whom the benefit-risk can be adequately characterized. The benefit-risk profile of certolizumab pegol is favorable to support both the 200 mg Q2W and the 400 mg Q4W chronic dosing regimens (with the same loading dose of certolizumab pegol 400mg initially and at Weeks 2 and 4) for the treatment of adult patients with active nr-axSpA with objective signs of inflammation.

Certolizumab pegol would provide first treatment option in the US for patients with nr-axSpA who also have objective measures of inflammation.

The regulatory action for this supplement is Approval. No PMR/PMCs are warranted.

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15 Appendices

15.1. References

Ghosh N and Ruderman E. Nonradiographic axial spondyloarthritis: clinical and therapeutic relevance. *Arthritis Res Ther*. 2017; 19: 286-395.

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15.2. Financial Disclosure

Below are details regarding the financial disclosures provided by the Applicant for study AS0006. See Section 8.1.2 for details regarding the adequacy of the financial disclosures.

Covered Clinical Study (Name and/or Number): AS0006

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 125 Principal Investigators, 394 Sub-Investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
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: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in the 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)

15.3. AS0006 Schedule of Events

Table 59. Schedule of Study Assessments (Screening through Week 52 and FU)

Visit #	Scr	Scr day -5 to -3	1/BL	2	3	4	5	6	7	8	9H	10	11H	12	13H	14	15H	16	17H	18	19H	20	21H	22	23H	24	25H	26	27	28	
Week Protocol Activity	-6 weeks to -1 day		0	1	2	4	6	8	10	12	14H	16	18H	20	22H	24	26H	28	30H	32	34H	36	38H	40	42H	44	46H	48	50	52WD	FU [b]
Inclusion/ Exclusion criteria	X	X	X																												
Informed consent [a]	X																														
Demographic data	X																														
Medical history and procedure history (incl. axSpA history)	X																														
Vital signs [c]	X		X		X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X	X
Hematology/ urine/ biochemistry [d]	X		X [e]		X	X		X		X						X						X								X [e]	X
HBsAg/ antibodies to hepatitis C/HIV/ HLA-B27/ CKD-EPI	X [f]																														
CRP	X [g]	X			X	X		X		X		X		X		X		X		X		X		X		X		X		X	X
Pregnancy testing [h]	X		X																											X	X
PE [i]	X		X		X	X		X		X		X				X						X								X	X
Extra-articular assessments			X			X				X						X						X						X		X	

[Source: UCB, AS0006 Interim Clinical Study Report, Table 3-3. Dated Sep 24, 2018: page 50.]

Table 59 (cont.). Schedule of Study Assessments (Screening through Week 52 and FU)

Visit #	Scr	Scr day -5 to -3	1/BL	2	3	4	5	6	7	8	9H	10	11H	12	13H	14	15H	16	17H	18	19H	20	21H	22	23H	24	25H	26	27	28	
Week Protocol Activity	-6 weeks to -1 day		0	1	2	4	6	8	10	12	14H	16	18H	20	22H	24	26H	28	30H	32	34H	36	38H	40	42H	44	46H	48	50	52WD	FU[b]
Chest x-ray [j]	X																													X	
TB test [k]	X																													X	
TB questionnaire	X		X							X						X						X								X	
Sacroiliac joint x-ray [l]	X																													X	
MRI [m]	X									X																				X	
BASMI & spinal mobility [n]	X		X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
BASDAI	X		X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
BASFI			X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
SF-36			X			X				X						X						X						X		X	
ASQoL			X	X	X	X				X						X						X						X		X	
MOS Sleep Scale			X			X				X						X						X						X			
EQ-5D			X			X				X						X						X						X		X	
MASES			X	X	X	X		X		X		X				X				X				X				X		X	
Total and nocturnal spinal pain			X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
Swollen and tender joint counts			X			X				X						X						X								X	

[Source: UCB, AS0006 Interim Clinical Study Report, Table 3-3. Dated Sep 24, 2018: page 51.]

Table 59 (cont.). Schedule of Study Assessments (Screening through Week 52 and FU)

Visit #	Scr	Scr day -5 to -3	1/BL	2	3	4	5	6	7	8	9H	10	11H	12	13H	14	15H	16	17H	18	19H	20	21H	22	23H	24	25H	26	27	28	
Week Protocol Activity	-6 weeks to -1 day		0	1	2	4	6	8	10	12	14H	16	18H	20	22H	24	26H	28	30H	32	34H	36	38H	40	42H	44	46H	48	50	52WD	FU [b]
PhGADA			X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
PGADA			X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
Productivity			X			X				X						X						X						X		X	
Resources utilization [o]			X			X				X						X						X						X		X	
CZP plasma concentration/ anti-CZP Abs / Biomarker			X	X	X	X				X						X						X								X	X
Genetics/epigenetics			X							X																					
Gene expression and proteomics			X			X				X																				X	
Prior and Concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IXRS [p]	X		X		X	X	X	X	X	X		X		X		X		X		X		X		X		X		X	X	X	X
Study drug administration sc [q]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Subject training on self-injection [r]									X	X																					

[Source: UCB, AS0006 Interim Clinical Study Report, Table 3-3. Dated Sep 24, 2018: page 52.]

Table 60. Schedule of Alternative Study Assessments with OL CZP (after Discontinuation from DB Study Treatment)

Visit #	1 wdt	2 wdt	3 wdt				4 wdt						5 wdt			
Week Protocol Activity	0	2	4	6H	8H	10H	12	14H	16H	18H	20H	22H	24 and Q12W		52/WD	FU [a]
Vital signs [b]	X	X	X				X						X	Continue W24 assessments every 12 weeks until as close as possible to W52/WD of the original visit schedule. Subject was then to be invited to the final assessment visit at W52/WD [g]	X	X
Hematology/ urine/biochemistry	X [c,d]						X						X		X[d]	X
CRP	X						X						X		X	X
Pregnancy testing [e]	X														X	X
PE [f]	X		X				X						X		X	X
Extra-articular assessments							X						X		X	
TB test [h]															X	
TB questionnaire	X						X						X		X	
BASMI / Spinal mobility [i]	X		X				X						X		X	
BASDAI	X		X				X						X		X	
BASFI	X		X				X						X		X	
SF-36	X						X						X		X	
AsQoL	X						X						X		X	
MOS Sleep Scale	X						X						X		X	
EQ-5D	X						X						X		X	
MASES	X						X						X		X	

[Source: UCB, AS0006 Interim Clinical Study Report, Table 3-3. Dated Sep 24, 2018: page 55.]

Table 60 (cont.). Schedule of Alternative Study Assessments with OL CZP (after Discontinuation from DB Study Treatment)

Visit #	1 wdt	2 wdt	3 wdt				4 wdt						5 wdt			
Week Protocol Activity	0	2	4	6H	8H	10H	12	14H	16H	18H	20H	22H	24 and Q12W		52/WD	FU [a]
Total and nocturnal spinal pain	X		X				X						X		X	
Swollen and tender joint counts	X		X				X						X		X	
Patient's Global assessment	X		X				X						X		X	
Investigator's AS assessment	X		X				X						X		X	
CZP plasma concentration/ anti-CZP Abs/ Biomarker	X		X				X						X		X	X
Gene expression and proteomics [j]															X	
Telephone contact [k]					X				X		X					
Prior and Concomitant medication	X	X	X				X						X		X	X
AEs	X	X	X				X						X		X	X
IXRS	X	X	X				X						X		X	X
CZP administration sc	X[l]	X[l]	X[l]	X	X	X	X	X	X	X	X	X	X[m]			

[Source: UCB, AS0006 Interim Clinical Study Report, Table 3-3. Dated Sep 24, 2018: page 56-7.]

Table 61. Schedule of Alternative Study Assessments with Other Treatments (after Discontinuation from DB Study Treatment)

Visit #	**1 wdt**	**2 wdt**	**3 wdt**			
Week Protocol Activity	**0**	**12**	**24 and Q12W**	**Continue W24 assessments every 12 weeks until as close as possible to W52/WD of the original visit schedule. Subject was then invited to the final assessment visit at W52/WD ±4 weeks. [d]**	**52/WD**	**FU [a]**
Hematology/urine/biochemistry	X [b,c]					
CRP	X	X			X	X
Pregnancy testing [g]	X				X	X
PE	X					X
BASDAI	X	X			X	
BASFI	X	X			X	
Total and nocturnal spinal pain	X	X			X	
Swollen and tender joint counts					X	
Patient's Global assessment	X	X			X	
Investigator's AS assessment	X	X			X	
CZP plasma concentration/anti-CZP Abs/ Biomarker	X	X				X
Prior and Concomitant medication	X	X	X		X	X
AEs	X	X	X		X	X
IXRS [e]	X	X	X		X	X
Other treatment administration	X [f]	Followed the regimen of the particular alternative treatment. Telephone contact was performed on the discretion of the Investigator				

[Source: UCB, AS0006 Interim Clinical Study Report, Table 3-3. Dated Sep 24, 2018: page 59-60.]

15.4. Additional Results from AS0006

Table 62. Cumulative Number of Patients who Started OL CZP after Visit Week

	Placebo (N=158)	CZP 200 mg SC Q2W (N=159)
Week 2	0	0
Week 4	0	0
Week 6	0	0
Week 8	0	0
Week 10	0	0
Week 12	15	4
Week 14	38	8
Week 16	62	10
Week 18	65	10
Week 20	78	11
Week 22	78	11
Week 24	82	15
Week 26	85	15
Week 28	89	18
Week 30	89	18
Week 32	93	18
Week 34	93	18
Week 36	94	19
Week 38	94	20
Week 40	96	20
Week 42	96	20
Week 44	96	20
Week 46	96	20
Week 48	96	20
Week 50	96	20

Abbreviations: CZP=certolizumab pegol; SC=subcutaneously; Q2W=every two weeks
[Source: Statistical Reviewer]

Table 63. Individual components of ASDAS-MI at Week 52 based on all observed

Week 52	PBO Mean (SD)	CZP 200 mg SC Q2W Mean (SD)	Placebo (N=158)	CZP 200 mg SC Q2W (N=159)	Estimated Adj Diff (95% CI)
ASDAS	2.1 (1.0) (n=134)	1.9 (1.0) (n=134)	-1.7 (1.2) (n=134)	-2.0 (1.1) (n=138)	-0.2 (-0.4, -0.0)
Patient global	3.4 (2.5) (n=134)	2.9 (2.4) (n=134)	-3.3 (2.9) (n=134)	-3.9 (2.7) (n=138)	-0.5 (-1.0, 0.1)
BASDAI Q2: Back pain	2.9 (2.4) (n=134)	2.7 (2.4) (n=134)	-3.3 (3.1) (n=134)	-3.6 (3.0) (n=138)	-0.2 (-0.7, 0.4)
BASDAI Q3: Peripheral pain/swelling	3.6 (2.3) (n=134)	3.1 (2.5) (n=138)	-3.8 (2.5) (N=134)	-4.3 (2.5) (N=138)	-0.5 (-1.0, 0.1)
BASDAI Q6: Duration of morning stiffness	2.8 (2.4) (n=134)	2.4 (2.3) (n=138)	-3.4 (2.8) (N=134)	-4.2 (2.7) (N=138)	-0.5 (-1.0, 0.0)
CRP(mg/L)	6.4 (9.7) (n=135)	6.0 (14.7) (n=140)	-9.3 (17.8) (N=135)	-10.0 (21.2) (N=140)	-0.4 (-3.3, 2.5)

Abbreviations: CZP=certolizumab pegol; SC=subcutaneously; Q2W=every two weeks; CI=confidence intervals; ASDAS=Ankylosing Spondylitis Disease Activity; CRP=C-reactive protein; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; n=number of patients with observed data
[Source: Statistical Reviewer]

Table 64. SF-36 value and its Components at Week 52 based on Observed Data

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At Week 52	PBO Mean (SD)	CZP Mean (SD)	PBO Mean Change from baseline (SD)	CZP Mean Change from baseline (SD)	Est Adjusted Diff (95% CI) p-value
SF-36 PCS	43.7 (8.4) (n=133)	46.6 (8.3) (n=137)	9.9 (8.2) (n=132)	11.7 (8.7) (n=136)	2.2 (0.4, 4.0) 0.02
Bodily Pain	45.3 (9.1) (n=133)	47.1 (9.2) (n=137)	11.5 (9.6) (n=132)	13.7 (9.9) (n=136)	1.8 (-0.3, 3.8) 0.10
General Health	40.9 (8.7) (n=133)	44.8 (9.1) (n=137)	4.7 (8.3) (n=132)	6.2 (9.3) (n=136)	2.6 (0.6, 4.5) 0.01
Physical Function	46.5 (9.3) (n=133)	48.5 (8.6) (n=137)	10.7 (9.0) (n=132)	12.0 (9.3) (n=136)	1.6 (-0.2, 3.4) 0.09
Role-Physical	43.1 (8.6) (n=133)	45.3 (8.0) (n=137)	8.4 (9.1) (n=132)	9.9 (8.8) (n=136)	1.8 (-0.003 3.6) 0.05
SF-36 MCS	47.5 (10.3) (n=133)	47.8 (10.7) (n=137)	6.1 (9.5) (n=132)	5.9 (11.7) (n=136)	0.1 (-2.1, 2.3) 0.92
Mental Health	45.9 (9.9) (n=133)	47.0 (10.1) (n=137)	6.2 (9.5) (n=132)	7.9 (11.7) (n=136)	1.4 (-0.7, 3.6) 0.19
Role-Emotional	47.4 (9.7) (n=133)	47.7 (9.4) (n=137)	6.5 (10.2) (n=132)	6.0 (11.0) (n=136)	0.1 (-1.9, 2.1) 0.93
Social Function	46.7 (9.7) (n=133)	47.8 (10.0) (n=137)	9.8 (9.9) (n=132)	9.8 (11.5) (n=136)	0.6 (-1.5, 2.8) 0.56
Vitality	47.1 (10.8) (n=133)	48.3 (10.5) (n=137)	10.1 (9.8) (n=132)	9.4 (10.0) (n=136)	-0.1 (-2.4, 2.1) 0.93

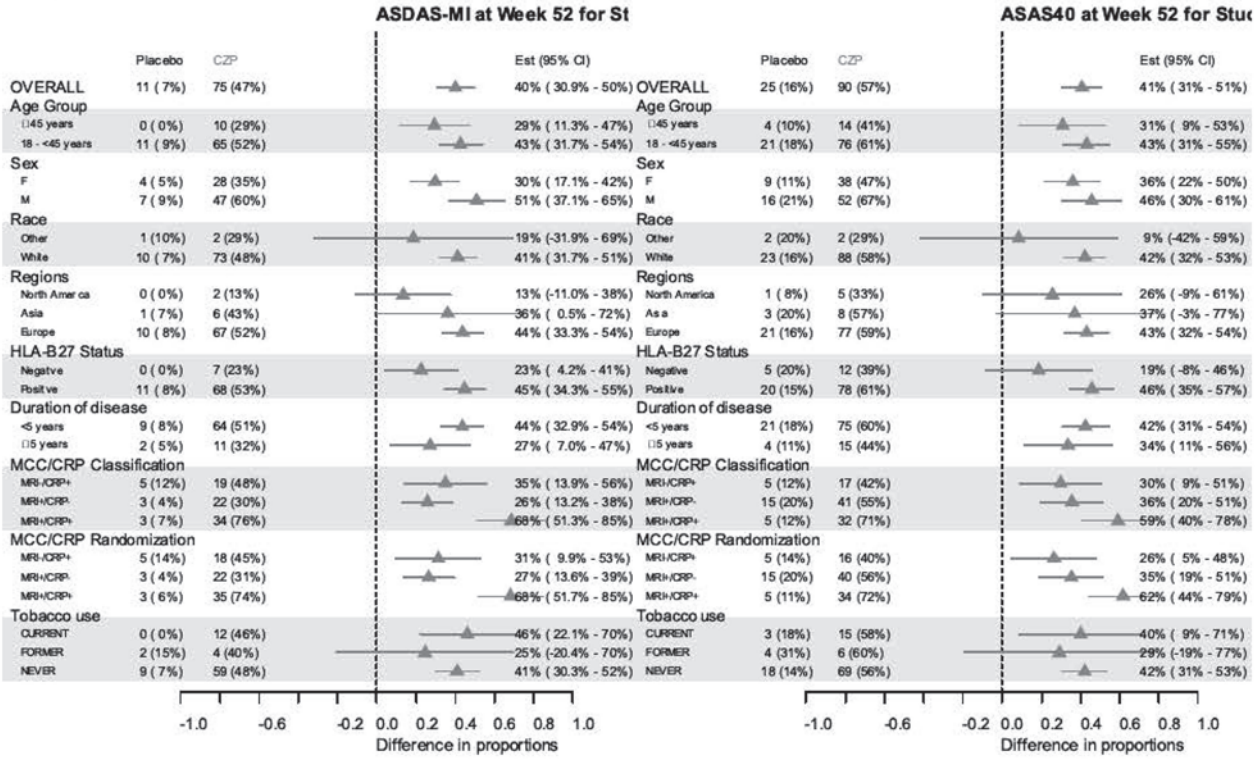
1: Difference in means comparing CZP with PBO, respective 95% CI, and p-value were estimated from a linear regression fit to the change from baseline in SF-36 component of interest adjusting to stratification factors, baseline SF-36 value.
Abbreviations: SF-36=Short-Form 36-Item Health Survey; PCS=Physical Component Summary; MCS=mental component summary; PBO=placebo; CZP=certolizumab pegol; SD=standard deviation; CI=confidence intervals; n=number of patients with observed data
[Source: Statistical Reviewer]

Table 65. SI Joint X-ray Evaluation for Patients with any Post Baseline X-ray Assessment

	PBO (N=158) Mean (SD)	CZP 200 mg SC Q2W (N=159) Mean (SD)
X-ray at baseline	0.40 (0.44) (n=69)	0.47 (0.48) (n=121)
X-ray at week 52	0.40 (0.48) (n=69)	0.45 (0.49) (n=121)
Days at X-ray evaluation	369 62 – 509	365 127 - 494

Abbreviations: PBO=placebo; CZP=certolizumab pegol; SD=standard deviation; n=number of patients with observed data
[Source: Statistical Reviewer]

Figure 10. Additional Subgroup Results for ASDAS-MI and ASAS40 at Week 52 Based on the Composite Estimand



[Source: Statistical Reviewer]

15.5. Additional Statistical Methodology Used in Review

Tipping Point Analysis Methodology

The goal is to evaluate the potential effect of violations in assumptions about missing data on the reliability of conclusions. Suppose that outcomes Y are independently distributed on the control and test drug arms. The parameter of interest is the difference in means θ. Consider the following parameterization and notation to describe the probabilities of completing the study (non-missingness), the true means in completers and dropouts, and the numbers of completers and total patients on the two treatment arms:

Table 66. Parameters and notation for tipping point analysis in presence of missing data.

Arm	Probability of non-missing	Mean among completers	Mean among dropouts	Number of completers	Sample size per arm
Placebo	π_c	μ_c	$\mu_c + \delta_c$	N_c	n_c
Treated	π_t	μ_t	$\mu_t + \delta_t$	N_t	n_t

Given this parameterization, the target of inference is $\theta = [\pi_t\mu_t + (1 - \pi_t)(\mu_t + \delta_t)] - [\pi_c\mu_c + (1 - \pi_c)(\mu_c + \delta_c)] \equiv \mu_t + (1 - \pi_t)\delta_t - [\mu_c + (1 - \pi_c)\delta_c]$. An analysis based on completers will provide reliable inference on θ if the missing-at random assumption, i.e., the assumption that $\delta_c = \delta_t = 0$, is valid. We will perform sensitivity analyses that allow for the possibility that outcomes among dropouts are not missing-at-random by performing inference under different assumed values of the parameters δ_c and δ_t.

Denote M_{ij} to be an indicator that patient j on treatment i is a completer, i.e., his or her outcome is observed where $i = c, t$, and $j = 1, \cdots, n_i$. By assuming fixed values of sensitivity parameters δ_c and δ_t, an estimator of θ can be represented by

$$\hat{\theta} = \hat{\mu}_t + (1 - \hat{\pi}_t)\delta_t - [\hat{\mu}_c + (1 - \hat{\pi}_c)\delta_c]$$

where $\hat{\mu}_i = \frac{1}{N_i}\sum_{k=1}^{n_i} Y_{ik}|M_{ik} = 1$ is the sample mean in the completers and $\hat{\pi}_i = \frac{N_i}{n_i} \equiv \sum_{k=1}^{n_i} M_{ik}/n_i$ is the sample proportion of completers on the treatment arm i, with i taking values c or t.

The test statistic can be constructed as follows:

$$\frac{\hat{\theta} - \theta}{\sqrt{\frac{s_t^2}{N_t} + \frac{s_c^2}{N_c} + \frac{\delta_t^2\hat{\pi}_t(1 - \hat{\pi}_t)}{n_t} + \frac{\delta_c^2\hat{\pi}_c(1 - \hat{\pi}_c)}{n_c}}}$$

where s_i^2 is the sample variance of the outcome. Under suitable conditions, the sampling test statistic is asymptotically normal with mean 0 and standard deviation 1.

The Wald-based 100 (1-α)% confidence interval of the form $\hat{\theta} \pm z_{1-\alpha/2}\sqrt{\frac{s_t^2}{N_t} + \frac{s_c^2}{N_c} + \frac{\delta_t^2\hat{\pi}_t(1-\hat{\pi}_t)}{n_t} + \frac{\delta_c^2\hat{\pi}_c(1-\hat{\pi}_c)}{n_c}}$ can be constructed where z_q is the q quantile of the standard normal distribution.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Origs237

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 27, 2013
From	Sarah Yim, M.D. Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	125160 supplement 215 (AS); supplement 237 (other axial spondyloarthritis)
Applicant	UCB, Inc.
Date of Submission	December 17, 2012
PDUFA Goal Date	October 17, 2013
Proprietary Name / Established (USAN) names	Cimzia® / certolizumab
Dosage forms / Strength	200 mg lyophilized powder for reconstitution in single-use glass vial; 200 mg/mL solution in single-use prefilled syringe
Proposed Indication(s)	1. Active axial spondyloarthritis, including patients with ankylosing spondylitis
Recommended:	*1. Approval for ankylosing spondylitis, with revisions to proposed labeling* *2. Complete response for other axial spondyloarthritis*

1. Introduction

This is a review of supplemental biologic license application (sBLA) 125160, supplements 215 and 237, for Cimzia® (certolizumab) in active axial spondyloarthritis, including patients with ankylosing spondylitis. Although the indication was submitted together in supplement 215, the supplement was split to accommodate the potential for differing actions for the specific diagnosis of ankylosing spondylitis and the new proposed broader indication of axial spondyloarthritis.

Certolizumab is a pegylated anti-TNFα fab fragment which was approved in the second review cycle on April 22, 2008 for the treatment of adult patients with moderately to severely active Crohn's disease who have had inadequate response to conventional therapy. The recommended dose for the treatment of Crohn's disease is 400 mg (given as two subcutaneous injections of 200 mg) initially and at Weeks 2 and 4, followed by 400 mg every 4 weeks for maintenance. Certolizumab was approved for the treatment of moderately to severely active rheumatoid arthritis (RA) on May 13, 2009. The recommended dose for RA 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. Alternatively, 400 mg every 4 weeks could also be considered. Cimzia was

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just approved for the treatment of active psoriatic arthritis (PsA) on September 27, 2013, with the same dose recommendations as for RA. Certolizumab is available in a single-use vial (lyophilized powder for reconstitution, 200 mg) and prefilled syringe (PFS) of 200 mg/mL.

In this efficacy supplement, UCB is seeking approval for an expanded indication of axial spondyloarthritis, including ankylosing spondylitis (AS), on the basis of study AS001, a 24-week double-blind placebo-controlled study with a 110-week open-label extension period in 325 patients who met the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial spondyloarthritis (axSpA). The study was designed to enroll a sufficient number of patients with AS and without AS (which we will call non-radiographic axial spondyloarthritis or nr-axSpA, for consistency with terminology discussed at Advisory Committee) to allow for an assessment of these subgroups.

This application brings to the fore a number of questions about the expanded diagnostic population of nr-axSpA and the subgroup of patients being proposed to serve as a new indication for drug development programs. These questions were discussed in detail at a meeting of the Arthritis Advisory Committee Meeting on July 22 and 23, 2013 (see Section 9 below), and are also the focus of this review.

2. Background

The spondyloarthritides (also known as "spondyloarthropathies") are a group of inflammatory rheumatic disorders distinguished from rheumatoid arthritis (RA) by absence of rheumatoid factor, axial skeleton involvement, enthesitis, dactylitis, and extra-articular features such as uveitis and skin rash. Also, in contrast to RA, peripheral arthritis, when present, tends to be asymmetrical. The spectrum of diagnoses includes ankylosing spondylitis (AS)—the prototypical axial spondyloarthritis—along with psoriatic arthritis, inflammatory bowel disease-related arthritis, reactive arthritis, and other "undifferentiated" spondyloarthritides.

Since 2003, four Tumor Necrosis Factor (TNF) inhibitors have been approved for the treatment of ankylosing spondylitis: Enbrel® (etanercept), Remicade® (infliximab), Humira® (adalimumab), and Simponi® (golimumab). TNF inhibitor treatment has demonstrated efficacy for multiple aspects of clinical disease activity in AS, but it not yet known whether treatment has a beneficial effect on structural damage progression. The patient population studied in the respective clinical development programs for the AS indication were patients with established AS, as defined by the modified New York Criteria, which includes a radiologic criterion of sacroiliitis grade $\geq$2 bilaterally or grade 3-4 unilaterally.[1]

However, it may take years, from the onset of inflammatory back pain symptoms until the appearance of radiographic sacroiliitis; and patients' disease activity and severity is not contingent on the presence or absence of radiographic sacroiliitis. Furthermore, there are patients who may not ever exhibit radiographic changes in the SI joints or spine, but who

[1] Van der Linden et al., Arthritis Rheum 1984; 27(4):361-368

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otherwise have debilitating disease. Thus ASAS developed criteria for the classification of axial spondyloarthritis[2] with the intent of defining a broader population of patients with axial spondyloarthritis but who may not have radiographic changes, to allow for earlier identification of ankylosing spondylitis patients but also to allow for identification of patients who may have undifferentiated axial spondyloarthritis.

The ASAS criteria require patients to have back pain for at least three months and age of onset less than 45 years. In addition, patients should have either sacroiliitis on imaging (MRI or x-ray) along with at least 1 SpA feature or be HLA-B27 positive and have at least 2 other SpA features. SpA features include inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's disease or ulcerative colitis, good response to NSAIDs, family history of SpA, HLA-B27 positive, and elevated C-reactive protein (CRP).

Relevant Regulatory History

End-of-Phase 2 (EOP2) feedback was provided to UCB in February 2010 regarding the possibility of an axial spondyloarthritis (including AS) indication. At that time, UCB proposed a trial where patients would meet ASAS criteria and would have sacroiliitis documented by x-ray or MRI. In light of this proposal, FDA indicated at that time that it seemed reasonable to use the ASAS criteria to select a broader population of patients with axial SpA in order to capture patients with early AS.

A pre-sBLA meeting was held in June 2011. At this meeting, FDA expressed concerns regarding a lack of clarity in the axial spondyloarthritis indication, what entities would be encompassed, and whether patients could evolve into diagnoses for which the risk-benefit profile of treatment would be unfavorable. FDA indicated discussion of the proposed indication would likely occur in a public forum, such as an advisory committee meeting.

3. CMC/Device

- **General product quality considerations**

No CMC or device data were included in this submission. No changes to the currently approved presentations, manufacturing, or controls were proposed in this submission.

- **Facilities review/inspection**

Facilities inspections/review are up to date with no outstanding issues.

- **Other notable issues (resolved or outstanding)**

None.

[2] Rudwaleit et al. Ann Rheum Dis 2009; 68(6):777-783

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4. Nonclinical Pharmacology/Toxicology

No nonclinical data were submitted in this sBLA.

5. Clinical Pharmacology/Biopharmaceutics

No clinical pharmacology or biopharmaceutics data were submitted in this sBLA.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Primary clinical reviewer: Janet Maynard, M.D. M.H.S; Primary statistical reviewer: Yongman Kim, Ph.D.; Secondary statistical reviewer: Joan Buenconsejo, Ph.D.

Overview of the clinical program

UCB is seeking approval for an expanded indication of axial spondyloarthritis, including ankylosing spondylitis, on the basis of study AS001, a 24-week double-blind placebo-controlled study with a 110-week open-label extension period in 325 patients who met the ASAS classification criteria for axial spondyloarthritis (axSpA). The ASAS criteria were modified for use in this trial, as family history of SpA and good response to NSAIDs were not used as qualifying SpA feature criteria. The study was designed to enroll a sufficient number of patients with AS and non-radiographic axial spondyloarthritis (nr-axSpA) to allow for an assessment of these subgroups. The protocol called for 50% of patients fulfilling modified New York Criteria for AS. Of the remaining 50% of patients, at least 50% of them had to meet ASAS MRI imaging criteria, and the remainder could be enrolled on the basis of clinical criteria only. Patients were classified into subgroups based on screening x-rays of sacroiliac joints interpreted locally. At baseline, repeat x-rays of the sacroiliac joints were obtained and evaluated by central readers.

In addition to meeting ASAS criteria, patients were required to have active disease, which was defined by a Bath AS Disease Activity Index (BASDAI) of $\geq$4 (out of 10), spinal pain $\geq$4 (out of 10), elevated c-reactive protein (CRP), or sacroiliitis on magnetic resonance imagine (MRI). Also, patients needed to have had an inadequate response or intolerance to at least 1 non-steroidal anti-inflammatory drug (NSAID).

For the double-blind placebo-controlled period (through Week 24), patients were randomized 1:1:1 to certolizumab 200 mg subcutaneously (SC) every other week (following a loading

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regimen of 400 mg SC at Weeks 0, 2, and 4), certolizumab 400 mg SC every four weeks (following a loading regimen of 400 mg SC at Weeks 0, 2, and 4), or placebo. From Weeks 24 to 48, patients in the certolizumab treatment groups remained on their assigned dose regimen in a blinded fashion, and placebo patients were randomized to certolizumab at either 200 mg every other week or 400 mg every 4 weeks following the standard loading regimen. Placebo-treated patients were similarly randomized if they met criteria for "escape" at Week 16. After Week 48, patients remained on their assigned treatment in an open-label fashion for the duration of the extension period to 110 weeks.

An MRI imaging substudy was conducted at selected sites familiar with the MRI acquisition and scoring systems utilized for this study. Patients in the MRI substudy received MRI scans of the spine and sacroiliac (SI) joints at baseline, Week 12, Week 48, and Week 96 (or withdrawal visit).

Brief Description of Efficacy Endpoints

The primary efficacy endpoint for study AS001 was the proportion of patients having an Assessment in Ankylosing Spondylitis (ASAS) 20 response at Week 12.

ASAS20 response is defined as an improvement of at least 20% and an absolute improvement of at least 1 unit (on a scale of 0 to 10) in at least 3 of 4 domains, and no worsening in the remaining domain:

- patient global assessment (numeric rating scale [NRS], 0 to 10)
- total back pain (NRS, 0 to 10)
- function as assessed by the Bath AS Functional Index (BASFI)
- inflammation, as assessed using the last two stiffness assessments in the Bath AS Disease Activity Index (BASDAI)

The BASFI is a functional index based on the patient's assessment of his/her ability to perform 10 selected activities during the past week on a numeric rating scale (NRS) from 0 to 10, with 0 being easy and 10 being impossible. The overall BASFI score is the average of the 10 items. A visual analog scale (VAS) from 0 to 100 may be used instead, but the 0 to 10 scale was used for Study AS001.

The BASDAI is a 6-item disease activity index that includes patient ratings of fatigue, spinal pain, peripheral arthritis, enthesitis, intensity of morning stiffness, and duration of morning stiffness. Five of these items are rated from 0 to 10, with 0 being no activity and 10 being very severe. The duration scale is rated from 0 to 10, with 0 being 0 hours and 10 being 2 or more hours. The overall BASDAI score is calculated as the sum of the values of questions 1 to 4, added to the average of questions 5 and 6 (intensity and duration of morning stiffness), and the total then divided by 5.

Multiple other endpoints were pre-specified in the study and are described in detail in the clinical and statistical reviews.

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Study Population

As previously mentioned, study AS001 enrolled adult patients meeting ASAS axial SpA classification criteria (with the exception that family history of SpA and good response to NSAIDs were not used as qualifying SpA features) and who have had an inadequate response or are intolerant to at least 1 NSAID. In addition to meeting ASAS criteria, patients were required to have active disease, which was defined by a Bath AS Disease Activity Index (BASDAI) of $\geq$4 (out of 10), spinal pain $\geq$4 (out of 10), elevated c-reactive protein (CRP), or sacroiliitis on magnetic resonance imagine (MRI).

The design of study AS001 allows for an internal comparison between AS and nr-axSpA subgroups. Selected baseline characteristics of these groups are summarized in Table 1 below. The demographic characteristics of AS and nr-axSpA patients were largely similar with one major exception being the gender balance. As expected, males predominate in the AS subgroup, comprising approximately 72-73% of the population. In the nr-axSpA subgroup, the male:female ratio is roughly equal. Both AS and nr-axSpA populations were predominantly HLA B-27 positive, although the proportions were slightly lower in the nr-axSpA group. Age and back pain duration were higher in AS vs. nr-axSpA. Baseline BASFI and CRP levels suggested more functional impairment and inflammation in the AS group vs. the nr-axSpA group. However, baseline back pain severity and BASDAI scores were similar between the AS and nr-axSpA subgroups.

In the MRI sub-study (n=153), patients' spine activity was evaluated using the Ankylosing Spondylitis spine MRI score for activity (ASspiMRI-a) using the Berlin modification. Sacroiliac joint activity was assessed using the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system. At baseline, the mean SPARCC score was 12.47 in the AS subgroup and 13.44 in the nr-axSPA subgroup. The mean baseline ASspiMRI score was 5.82 in the AS subgroup and 3.7 in the nr-axSpA subgroup.

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Table 1: Selected Baseline Characteristics of the AS and Nr-axSpA Subgroups in Study AS001

Characteristic	PBO	CZP 200mg Q2W	CZP 400mg Q4W
Overall axial SpA population, N	107	111	107
AS Subgroup, N	57	65	56
Age (years)			
Median (range)	41.0 (21, 68)	39.0 (24, 64)	41.5 (19, 66)
Gender, n (%)			
Male	41 (71.9)	47 (72.3)	41 (73.2)
Female	16 (28.1)	18 (27.7)	15 (26.8)
HLA B-27 positive, n (%)	48 (84.2)	53 (81.5)	44 (78.6)
Back pain duration (yrs)			
Mean (SD)	13.1 (10.8)	10.5 (8.8)	12.4 (10.1)
Median (range)	10.2 (0.3, 50.9)	8.8 (0.3, 32.7)	8.8 (0.3, 44.8)
Back pain severity (0-10)			
Mean (SD)	7.3 (1.6)	7.0 (2.3)	6.9 (1.6)
Median (range)	7.0 (4.0, 10.0)	7.0 (0.0, 10.0)	7.0 (3.0, 10.0)
BASDAI			
Mean (SD)	6.4 (1.8)	6.5 (1.7)	6.2 (1.3)
BASFI			
Mean (SD)	6.0 (2.0)	5.6 (2.3)	5.7 (2.3)
CRP (mg/L)			
Mean (SD)	25.2 (26.7)	20.5 (27.2)	18.3 (23.0)
Median (range)	16.6 (1.4, 155.6)	14.0 (0.1, 174.8)	12.9 (0.7, 159.9)
Nr-axSpA subgroup, N	50	46	51
Age (years)			
Median (range)	37.0 (19, 68)	33.0 (20, 78)	37.0 (20, 67)
Gender, n (%)			
Male	24 (48.0)	20 (43.5)	27 (52.9)
Female	26 (52.0)	26 (56.5)	24 (47.1)
HLA B-27 positive, n (%)	39 (78.0)	34 (73.9)	37 (72.5)
Back pain duration (yrs)			
Mean (SD)	9.2 (10.0)	8.5 (9.1)	8.1 (6.8)
Median (range)	4.5 (0.5, 41.5)	4.8 (0.3, 34.2)	7.3 (0.3, 25.3)
Back pain severity (0-10)			
Mean (SD)	6.8 (2.1)	7.2 (1.7)	6.9 (2.0)
Median (range)	7.0 (1.0, 10.0)	7.0 (3.0, 10.0)	7.0 (2.0, 10.0)
BASDAI			
Mean (SD)	6.4 (1.4)	6.4 (1.4)	6.6 (1.6)
BASFI			
Mean (SD)	4.9 (2.2)	4.8 (2.2)	5.1 (2.2)
CRP (mg/L)			
Mean (SD)	19.1 (25.0)	13.4 (11.8)	15.5 (19.2)
Median (range)	13.5 (0.2, 156.2)	10.0 (2.0, 52.0)	12.1 (0.1, 120.0)

AS=ankylosing spondylitis; CZP=certolizumab; nr-axSpA=nonradiographic axSpA; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks;
Source: Adapted from Tables 15 and 17 of Dr. Maynard's Clinical Review

Of note, given the challenges of reading plain films for sacroiliitis, there was some discordance between local and central interpretation of the screening and baseline x-rays, respectively. Local assessment of screening x-rays was used to identify the subgroups in study AS001. Most patients subsequently received a baseline x-ray, which was read by a central reader and

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evaluated for consistency with the screening x-ray interpretation. As shown in Table 2, approximately half of the patients identified as not having radiographic sacroiliitis meeting the modified New York criteria by the local reader were identified as meeting those criteria by the central reader. Discordance was less for patients identified as having AS by the local reader; 21% of those patients were not felt to meet the modified New York radiographic criterion by the central reader. Based on the central reader assessment, 184 patients had AS and 98 patients had nr-axSpA in study AS001. Forty-three patients did not have centrally read x-rays.

Table 2: Comparison of local and central reader assessments of sacroiliac x-rays

Local assessment (screening)	Central reader's assessment (baseline)†		
	mNY-Yes n (% concordance or discordance)	mNY-No n (% concordance or discordance)	No Central Read N
mNY-Yes (N=178)	112 (79)	29 (21)	37
mNY-No (N=147)	72 (51)	69 (49)	6
Total, n	184	98	43

† Central reads were not performed for 43 patients as x-rays were not available.
mNY=modified New York Criterion
Yes=fulfilling modified New York Criterion for ankylosing spondylitis
No=not fulfilling the modified New York Criterion for ankylosing spondylitis
Source: Adapted from Table 21 of Dr. Maynard's Clinical Review and Table 7 of Dr. Kim's Statistical Review

Efficacy findings

The primary endpoint for study AS001 was the proportion of ASAS20 responders in the overall axial spondyloarthritis population at Week 12. As summarized in Table 3 below, certolizumab treatment was associated with approximately 20% more ASAS20 responders than placebo.

Table 3: Primary Endpoint: ASAS20 response at Week 12 in overall axial SpA population (RS)

	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W + CZP 400mg Q4W
Overall axSpA population, N	107	111	107	218
Responders (%)	38	58	64	61
Difference to PBO (%)	---	19	25	22
P-value	---	0.004	<0.001	<0.001

ASAS20=ASsessment in Axial Spondyloarthritis International Society 20% response criteria; axial SpA=axial spondyloarthritis; CI=confidence interval; CZP=certolizumab; –=not applicable; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set
Source: Adapted from Table 23 of Dr. Maynard's Clinical Review

Analyses were performed to explore the treatment effect in the AS and nr-axSpA subgroups, and also to explore the impact of differences between local and central x-ray reads used to classify the subgroups; as summarized in Table 4 below. The treatment difference in the proportion of responders in the certolizumab treatment arms vs. the placebo arm approximates

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20% in most subgroups, irrespective of subgroup or x-ray reader, and is consistent with the overall trial population. However, the absolute proportion of responders in the centrally-read nr-axSpA subgroup is lower than in the other analyses; the treatment difference is consistent due to having a lower proportion of placebo responders in the subgroup as well. The subgroup of patients having no centrally-read baseline x-rays is also included for completeness. Thirty-seven of these 43 patients were identified as meeting criteria for AS by the local reader interpretation of screening x-rays.

Table 4: ASAS20 responses at Week 12 in AS and nr-axSpA subgroups by local and central x-ray interpretation status

	PBO	CZP 200mg Q2W	CZP 400mg Q4W
LOCAL READ			
AS subgroup, N	57	65	56
Responders (%)	37	57	64
Difference to PBO (%), (95% CI)	---	20 (3, 37)	27 (10, 45)
nr-axSpA subgroup, N	50	46	51
Responders (%)	40	59	63
Difference to PBO (%), (95% CI)	---	19 (-1, 38)	23 (4, 42)
CENTRAL READ			
AS subgroup, N	57	66	61
Responders (%)	46	61	69
Difference to PBO (%), (95% CI)	---	15 (-3, 32)	23 (6, 41)
nr-axSpA subgroup, N	35	33	30
Responders (%)	20	42	47
Difference to PBO (%), (95% CI)	---	22 (1, 44)	27 (4, 49)
NO CENTRAL READ			
N	15	12	16
Responders (%)	53	83	75
Difference to PBO (%), (95% CI)	---	30 (-3, 63)	21 (-11, 55)

AS=ankylosing spondylitis; ASAS20=Assessment in Axial Spondyloarthritis International Society 20% response criteria; CI=confidence interval; CZP=certolizumab; -=not applicable; nr-axSpA=nonradiographic axial spondyloarthritis; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set
Source: Adapted from Table 24 of Dr. Maynard's Clinical Review and Tables 5 and 8 of Dr. Kim's Statistical Review

It is not possible to draw definitive conclusions from these subgroup analyses. However, the consistency of the apparent treatment difference across subgroups suggests that the overall results are not being driven by a single subgroup, e.g., AS patients.

Results for the key secondary endpoints generally supported a similar conclusion, i.e., results do not appear to be driven by a single subgroup. However, depending on the endpoint, the magnitude of treatment effect, and whether the treatment effect was greater in the AS or nr-axSpA subgroup did appear to be affected by central or local x-ray interpretations. These analyses are discussed in detail in the primary clinical and statistical reviews.

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8. Safety

Certolizumab has a Boxed Warning for serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections, and infections due to opportunistic pathogens. The Boxed Warning also includes malignancy; especially lymphoma and hepatosplenic T-cell lymphoma. Certolizumab has Warnings and Precautions related to serious infections, malignancy, hypersensitivity reactions, Hepatitis B Virus reactivation, central and peripheral demyelinating disease, cytopenias, worsening of congestive heart failure, lupus-like syndrome, and against use with anakinra or abatacept.

- **Discuss the adequacy of the database, major findings/signals**

The safety data in the sBLA are derived from study AS001 through the 24-week placebo-controlled treatment period. In this study, 274 patients received at least one dose of certolizumab. Data from the ongoing 110-week extension period were not provided in this application. The median duration of exposure to certolizumab in the study was 20 weeks (range 4 to 25 weeks). The size of other clinical development programs for AS and nr-axSpA is summarized in Table 5 below, for reference. Relative to other programs supporting approval in AS, the safety database for this application is somewhat smaller, as the total number of patients is divided among AS and nr-axSpA.

Table 5: Size of Clinical Development Programs for AS and nr-axSpA

Drug (indication)	*Total, N*	*Dose 1, N*	*Dose 2, N*	*Placebo, N*
Golimumab (AS)	356	138	140	78
Infliximab (AS)	279	201	--	78
Etanercept (AS)	277	138	--	139
Adalimumab (AS)	315	208	--	107
Adalimumab (nr-axSpA)	185	94	--	91
Certolizumab				
Total with axSpA	325	111	107	107
AS	178	65	56	57
Nr-axSpA with inflammation	147	46	51	50

Source: Table 35 of Dr. Maynard's Clinical Review

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests**

Deaths

In study AS001, there were no deaths during the 24-week controlled period.

Serious Adverse Events (SAE)

A similar proportion of patients (approximately 5%) in the placebo and certolizumab groups experienced serious adverse events (SAEs), although the only serious infections (appendicitis, esophageal candidiasis, haemophilus infection, and laryngitis) occurred in certolizumab-

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treated patients. There were no opportunistic infections or cases of tuberculosis in the 24-week controlled period; however one case of TB was reported in the 120-day safety update. There were no malignancies reported during the 24-week controlled period.

Discontinuations due to Adverse Events

Two patients discontinued from the placebo group, two patients discontinued from the CZP 200 mg q2w group (due to infection of folliculitis and upper respiratory tract infection), and four patients discontinued from the CZP 400 mg q4w group (cholelithiasis, hypersensitivity, increased CRP reported at an early termination visit, gynecomastia).

Common Adverse Events

A higher proportion of CZP-treated patients (~75%) reported an adverse event compared to placebo-treated patients (~63%). The most common adverse events reported in the CZP treatment groups were nasopharyngitis (9%), headache (6%), creatine phosphokinase increased (5%), rash (4%) and upper respiratory tract infection (4%).

Laboratory Abnormalities

Certolizumab-treatment was associated with a small increased incidence of liver enzyme abnormalities and leukopenia. This is consistent with other TNF inhibitors and what was observed with certolizumab in other indications. Certolizumab-treatment was also associated with a small increased incidence of creatine phosphokinase (CPK) elevation that did not appear to be associated with clinical events.

- **Immunogenicity**

Ten of 274 (~4%) of patients tested positive for anti-certolizumab antibodies after certolizumab exposure, which is within the incidence observed in other certolizumab trials. There did not appear to be a relationship between immunogenicity status and adverse events.

- **Special safety concerns**

As noted above, there were few serious infections and no malignancies in the safety database through the data cutoff date. There were no cases of demyelinating disease. One patient developed pustular psoriasis during the 24-week double-blind period, but no other additional autoimmune disorders were reported.

- **Safety conclusions**

Dr. Maynard has concluded that no new safety signals were identified in study AS001, and that certolizumab appeared to exhibit a safety profile consistent with the approved product label, and I concur.

- **Discussion of notable safety issues (resolved or outstanding).**

Overall, the safety profile of certolizumab in this submission appeared to be consistent with the known safety profile of certolizumab; however, the data are limited. Based on central interpretation of baseline x-rays, there could be as few as 98 patients with nr-axSpA in the study and only data from 24 weeks of study AS001 were submitted. The amount of data that would support the indication is even lower as additional subgrouping is applied for the proposed broader indication (see Section 9 below). Thus, although the safety data available did not identify new safety concerns, there are insufficient data to characterize the safety profile of the non-AS patients that the applicant is proposing for the broader indication.

9. Advisory Committee Meeting

A two-day meeting of the Arthritis Advisory Committee (AAC) was held on July 22 and 23, 2013. The topic on the first day was a general discussion of the ASAS classification criteria for axial spondyloarthritis, and the potential implications of using these criteria to define an indication for drug approval. The second day was a product-specific discussion of the sBLAs for adalimumab in non-radiographic axial spondyloarthritis and certolizumab for axial spondyloarthritis, including ankylosing spondylitis (this application).

Regarding the general discussion of the ASAS classification criteria for axial spondyloarthritis, Committee members noted that longer-term data are needed to understand the natural history of the populations that would be included by the ASAS criteria, but did not feel this would preclude use of axial spondyloarthritis as an indication before those data were available. A more pressing concern was the potential for misclassification of patients with mechanical back pain, as one could potentially meet the ASAS criteria by having relatively non-specific clinical criteria, such as back pain for more than 3 months, being HLA-B27 positive, with a family history of axial spondyloarthritis, and good response to NSAIDs. To address this concern, the majority of the panel felt that use of objective measures of inflammation would be helpful, and in particular, MRI of the sacroiliac joints.

On July 23, 2013, DPARP and the Sponsor discussed the findings from the certolizumab sBLA at the afternoon session of the Arthritis Advisory Committee meeting. The committee members were divided on whether the data provided substantial evidence that certolizumab provides a clinically meaningful beneficial effect in the treatment of active axial spondyloarthritis, including patients with ankylosing spondylitis (8 yes, 5 no, 1 abstain). The committee members commented that the definition of “active” axial spondyloarthritis was unclear and it was uncertain whether the small number of patients exposed is sufficient enough to support a new indication. The majority of the committee members felt that safety profile was adequate to support approval of certolizumab for active axial SpA (13 yes, 1 no, 1 abstain) due to lack of new safety signals identified in axial SpA. Members did express concerns regarding serious infection and CK elevations. Regarding the overall approval question, the committee was divided regarding whether there were adequate safety and efficacy data to support approval of certolizumab for the treatment of active axial SpA (7 yes, 6 no, 1 abstain).

Reference ID: 3380720

During discussion of the questions, multiple panel members expressed concerns regarding the ability to characterize patients into the subgroups of AS and nr-axSpA due to limitations in x-ray classification. Further, some members noted that the number of patients studied was small and more data and clarity on the definition of active axial SpA was needed.

10. Pediatrics

The applicant submitted a full waiver request for pediatric patients based on the rationale that studies would be impossible or impractical due to the rarity of specific axial spondyloarthritis diagnoses in children. The Agency has previously waived studies for juvenile equivalents of AS based on a similar rationale. This waiver request was discussed with the Pediatric Review Committee (PeRC) on August 14, 2013, and PeRC agreed with granting a full waiver.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** Not applicable
- **Exclusivity or patent issues of concern:** Not applicable
- **Financial disclosures:** No issues
- **Other GCP issues:** No issues
- **DSI audits:** No issues or concerns were identified that would warrant clinical study site inspections; therefore inspections were not requested for this efficacy supplement.
- **Other outstanding regulatory issues:** None

12. Labeling

- **Proprietary name**—already approved as Cimzia.
- **Physician labeling**

The applicant's initially proposed indication was "Treatment of active axial spondyloarthritis, including ankylosing spondylitis." After the Advisory Committee discussions, the applicant propose (b) (4)

(b) (4)

After a teleconference on September 9, 2013, where the review team discussed the remaining concerns with the broader axial spondyloarthritis indication and reservations regarding the ability of the currently submitted data to support approval of a broader indication, the applicant submitted a third indication proposal as follows:

(b) (4)

The difficulty with this proposed indication is that it is unclear how many patients in AS001 actually fit the description of the latter part of this indication [redacted] (b) (4) The concerns the review team has regarding the adequacy of the submitted data to support a specific subgroup of non-AS patients for a broader indication remain, and cannot be addressed by labeling alone.

- **Carton and immediate container labels**—already approved; no changes in marketed presentations were proposed.
- **Patient labeling/Medication guide**—Patient labeling and a Medication Guide are currently approved for Cimzia.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval for the indication of ankylosing spondylitis. I recommend a complete response for a broader indication of axial spondyloarthritis patients who do not have definitively diagnosed AS.

- **Risk Benefit Assessment**

This sBLA raised a number of concerns:

- Certolizumab has not previously been approved for ankylosing spondylitis, so the limited data available from study AS001 is being proposed to support an indication for AS as well as the broader nr-axSpA population.
- Based on central reader interpretations of sacroiliac x-rays, there could be as few as 98 patients with nr-axSpA in study AS001, and the subgroup of patients that would be described by the proposed indications (See Section 9 above) is a fraction of this number. It is uncertain whether the results from study AS001 would accurately describe the efficacy and safety of certolizumab in the population of non-AS patients proposed for the indication if this population were prospectively identified and studied.
- Also, based on central reader interpretation, the nr-axSpA subgroup was associated with a lower proportion of ASAS20 responders compared to the AS subgroup. Although the treatment difference was similar due to also having a lower proportion of placebo responders in the subgroup, this raises a question regarding the actual level of benefit that certolizumab-treatment would be expected to have in nr-axSpA patients.
- There is still uncertainty regarding what disease entities are being captured by the nr-axSpA classification. Demographics in the subgroups of study AS001 show that nr-axSpA patients include a similar number of males and females, whereas AS is male predominant. Data have not been provided regarding the natural history of nr-axSpA patients and whether the risk-benefit profile of treatment would be expected to remain the same over

time (e.g., chronic immunosuppressive therapy may not be warranted if patients might be expected to remit).

In light of these concerns, it is not possible to form definitive conclusions regarding the benefit-risk profile of certolizumab for axial spondyloarthritis patients other than those definitively diagnosed with AS.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

Not applicable.

- **Recommendation for other Postmarketing Requirements and Commitments**

Not applicable.

- **Recommended Comments to Applicant**

The submitted data from study AS001 are inadequate to support approval of certolizumab at a dose of 200 mg subcutaneously every other week or 400 mg subcutaneously every four weeks for the treatment of patients with axial spondyloarthritis other than ankylosing spondylitis. The populations proposed for a broader axial spondyloarthritis indication are subgroups of the overall study population who have not been studied adequately to demonstrate efficacy and safety.

To support approval of Cimzia for a broader axial spondyloarthritis indication, provide efficacy and safety data from at least one controlled 12-month trial in patients who are clearly identified to have non-radiographic axial spondyloarthritis. Exclude patients with ankylosing spondylitis from the study. Ensure adequate representation of patients in each of these groups: positive MRI findings at the sacroiliac joints, elevated CRP at baseline, and both positive MRI findings at the sacroiliac joints and elevated CRP at baseline. Consider other factors that may impact the effect of treatment, such as duration of disease, and prior use of therapy. Develop and submit plans for risk mitigation and safe use of Cimzia in the targeted population.

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/s/

SARAH K YIM
09/27/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Origs237

CLINICAL REVIEW(S)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUZETTE W PENG
12/06/2018

RACHEL GLASER
12/06/2018

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125160/215 and 237
Priority or Standard	Standard
Submit Date(s)	December 17, 2012
Received Date(s)	December 17, 2012
PDUFA Goal Date	October 17, 2013
Division / Office	DPARP
Reviewer Name(s)	Janet Maynard, MD, MHS
Review Completion Date	August 23, 2013
Established Name	Certolizumab
Trade Name	Cimzia®
Therapeutic Class	Immunosuppressant
Applicant	UCB
Formulation(s)	Subcutaneous
Dosing Regimen	After an initial loading dose of 400mg at weeks 0, 2, and 4, administer 200mg every other week or 400mg every 4 weeks subcutaneously
Indication(s)	Active axial spondyloarthritis, including patients with ankylosing spondylitis
Intended Population(s)	Adult patients

Template Version: March 6, 2009

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1 RECOMMENDATION/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

In the original submission, the supplemental biologic license application (sBLA) 125160/215 was certolizumab for the treatment of active axial spondyloarthritis (axial SpA) including ankylosing spondylitis (AS). During the review, it was determined that the sBLA should be split into two supplements: AS and non-radiographic axial SpA (nr-axSpA). While the term "axial SpA" encompasses both AS and nr-axSpA, there is no regulatory precedent for approval of an indication for the broader diagnosis "axial SpA" or the narrower diagnosis nr-axSpA. Thus, it was felt that it was more appropriate to split the sBLA based on the two indications encompassed within the initially proposed indication: axial SpA.

The clinical recommendation for sBLA 125160/215, certolizumab for the treatment of active AS, is **approval**. This recommendation is based on adequate evidence of efficacy and safety for the proposed indication. The clinical recommendation for sBLA 125160/237, certolizumab for the treatment of active nr-axSpA, is **complete response**. This recommendation is based on inadequate evidence of efficacy and safety in the proposed population.

To support these applications, the Sponsor submitted data from one clinical study in active axial SpA patients. The study (AS001) consisted of a 24 week double-blind period followed by an open label extension. The Sponsor submitted data to Week 24. During the double-blind period, 325 patients were randomized (1:1:1) to certolizumab 200mg every 2 weeks (Q2W), certolizumab 400mg every 4 weeks (Q4W), or placebo. During the open label extension, al patients received certolizumab. Patients were included who met the Assessment of Spondyloarthritis international Society (ASAS) criteria for axial SpA, which includes patients with AS and nr-axSpA. Patients were categorized as having AS or nr-axSpA at screening when local investigators evaluated sacroiliac x-rays and clinical features. Additional sacroiliac x-rays were obtained at baseline and were read centrally. Based on central evaluation, there appeared to be significant misclassification, especially for patients with nr-axSpA. Based on central x-ray evaluation, the majority of the patients in the study had AS. The number of patients who did not have imaging evidence of sacroiliitis is unclear as magnetic resonance imaging data were only available for a subset of patients. Thus, limited data were available to support the nr-axSpA indication.

From an efficacy and safety perspective, study AS001 provided sufficient data to support the use of certolizumab for AS. However, for nr-axSpA, limited data were available, especially for patients without imaging evidence of sacroiliitis.

1.2 Risk Benefit Assessment

Introduction

This document provides a clinical review of certolizumab (Cimzia®) for the proposed indication of active axial spondyloarthritis (SpA), including ankylosing spondylitis (AS). Initially, this was a single supplement. However, the sBLA was split into two supplements: AS and non-radiographic axial SpA (nr-axSpA). While the term "axial SpA" encompasses both AS and nr-axSpA diagnoses, there is no regulatory precedent for approval of an indication for the broader diagnosis axial SpA or the narrower diagnosis nr-axSpA.

Certolizumab is a monoclonal antibody Fab' fragment that binds to tumor necrosis factor (TNF) alpha. Elevated TNF is thought to play an important role in inflammation and joint destruction that occurs in a variety of forms of inflammatory arthritis, including RA, juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), and AS. The efficacy and safety of certolizumab has been established in one form of inflammatory arthritis: RA. Certolizumab does not currently have an indication for AS.

Background on the Proposed Indication: Axial Spondyloarthritis

The Sponsor's proposed indication is axial spondyloarthritis (SpA), including patients with ankylosing spondylitis (AS). Axial SpA encompasses a spectrum of disease severity that spans from self-limited inflammation to bony destruction of the spine. AS is a well-characterized, chronic and progressive form of axial SpA. The majority of research performed over the last two decades has used the modified New York Critieria[1] to identify patients with AS (Table 1). Further, these criteria were used in the clinical trials performed to support product registration in AS. In contrast to previous registration programs for the more limited population of patients with AS, the current Sponsor proposes registration for the broader population of patients with axial SpA.

Table 1: Modified New York criteria for ankylosing spondylitis

Clinical Criteria • Low Back pain and stiffness for longer than 3 months, which improve with exercise, but are not relieved by rest • Restriction of motion of the lumbar spine in both the sagittal and frontal planes • Restriction of chest expansion relative to normal values correlated for age and sex
Radiologic criterion • Sacroiliitis grade ≥2 bilaterally, or grade 3-4 unilaterally
Definitive ankylosing spondylitis is present if the radiologic criterion is associated with at least one clinical criterion

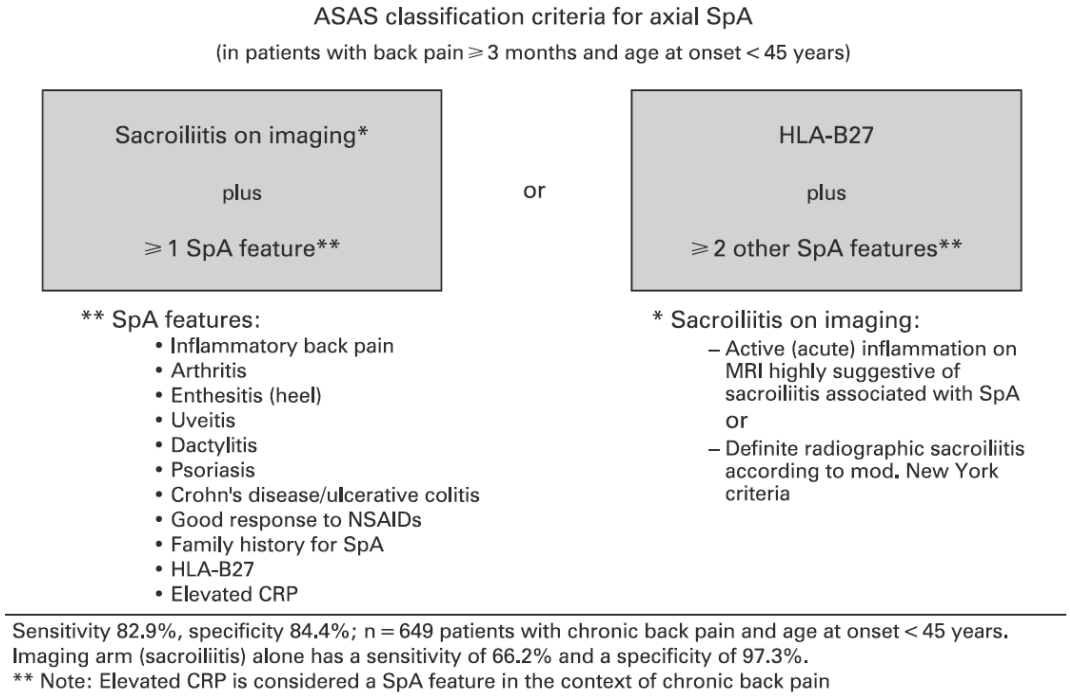
Source: van der Linden S. Arthritis Rheum 1984;27(4):361-8.

The modified New York Criteria[1] have potential limitations in clinical practice as they are designed to identify patients with established AS and do not identify all patients in the larger spectrum of inflammatory back pain. Although the long-term benefit of early treatment in AS, with respect to disease progression, remains unclear, the Assessment

of Spondyloarthritis international Society (ASAS) developed criteria for axial SpA with the goal of identifying more patients in the spectrum of inflammatory back pain, including patients with early AS[2, 3]. By design, these criteria were meant to be inclusive, as not to miss patients with the potential for developing progressive disease. As a result, the ASAS criteria identify a heterogeneous group of patients as described below.

The ASAS criteria for axial SpA require patients to have back pain for at least three months and age of onset less than 45 years. Subsequently, patients must meet clinical or imaging criteria (Figure 1). The imaging criteria include evidence of sacroiliitis on magnetic resonance imaging (MRI) or x-ray and at least one additional clinical feature. The clinical criteria include the presence of HLA-B27 and at least two other SpA features. The clinical SpA features include inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease or ulcerative colitis, good response to NSAIDs, family history for SpA, HLA-B27, and elevated CRP. As a consequence of being more inclusive, the criteria increase the heterogeneity of the resulting disease group and may reduce the utility of these criteria for drug development.

Figure 1: ASAS classification criteria for axial SpA



Source: Rudwaleit. M Ann Rheum Dis 2009;68(6):777.

We acknowledge that there is debate within the AS research community regarding the nomenclature for the spectrum of inflammatory diseases encompassed by the term axial SpA. Some authors have argued that the term AS should be retained because axial SpA cases have far greater clinical heterogeneity than AS and have broader etiologies[5]. For the purposes of this document we will use the definitions and terms

listed in Table 2.

Table 2: Definitions and terms used in this document

Term	Definition of this term as used in this document
Axial spondyloarthritis (axial SpA)	Patients fulfilling the ASAS criteria[2-4] for axial spondyloarthritis
Ankylosing spondylitis (AS)	Patients fulfilling the modified New York criteria for AS[1]. Thus, patients with pelvis x-ray changes consistent with AS.
Non-radiographic axial spondyloarthritis (nr-axSpA)	Patients fulfilling the ASAS criteria[2-4] for axial spondyloarthritis, but without pelvis x-ray changes consistent with AS. Of note, these patients may have MRI changes suggestive of sacroiliitis.

Source: FDA generated

Data suggest that the entities nr-axSpA and AS might describe different patient populations due to differences in demographics, genetics, and response to treatment[5-10]. Further, limited data are available on the prevalence and natural history of nr-axSpA. To our knowledge, no prospective evaluations have been conducted to describe the natural history of nr-axSpA as defined by the ASAS classification criteria[2, 3]. While the natural history of nr-axSpA is unknown, patients with nr-axSpA can have significant pain and functional limitations secondary to their illness. Thus, clinical studies have evaluated treatment options, such as TNF-inhibitors, for nr-axSpA. It is unclear whether the risk/benefit profile of treating patients with nr-axSpA is different than the risk/benefit profile of treating patients with AS.

Overview of Clinical Program

The Sponsor submitted the results from one trial with a 24-week controlled portion as the primary basis for the efficacy and safety of certolizumab for the treatment of signs and symptoms of axial SpA:

- Trial AS001: Randomized, placebo-controlled, 24-week double-blind period followed by a 110-week open-label extension in patients with active axial SpA.

During the double blind period, 325 patients were randomized (1:1:1) to certolizumab 200mg every 2 weeks (Q2W), certolizumab 400mg every 4 weeks (Q4W), or placebo. The dose of certolizumab was based upon the approved dose of certolizumab for RA. Patients were included in the trial who met the ASAS classification criteria for axial SpA. The primary and secondary analyses were pre-specified in this overall population. Additional analyses were performed in the subgroups of patients with AS and nr-axSpA. Classification into one of these subgroups was based on screening x-rays of the sacroiliac joints. These x-rays were interpreted by local investigators. At baseline, repeat x-rays of the sacroiliac joints were obtained and were evaluated by central readers. Analyses comparing screening and baseline x-ray showed differences in patient classification, especially for patients classified by local investigators as not demonstrating radiographic evidence of AS.

Patients in trial AS001 had active disease, which was defined by having Bath AS Disease Activity Index (BASDAI) ≥4, spinal pain ≥4, and c-reactive protein (CRP) >the upper limit of normal (ULN) or sacroiliitis on MRI. In addition, patients needed to have been intolerant to or have had an inadequate response to at least 1 non-steroidal anti-inflammatory drug (NSAID).

The patient population was a major consideration during the review. While the Sponsor utilized the ASAS criteria for entry, patients had to have "active" disease as defined by the sponsor. In addition, there are analyses with different patient subgroups. All the variations in defining the patient population raise questions regarding whether axial SpA is understood well enough to support an indication.

Summary of Efficacy

Trial AS001 was submitted as the primary source of efficacy data for certolizumab in the treatment of axial SpA. The trial consisted of a 24-week double-blind period followed by a 110-week open label extension. The Sponsor submitted data to Week 24. The primary efficacy analysis was at Week 12. The primary endpoint was the proportion of patients with an ASessment in Ankylosing Spondylitis (ASAS) 20 response. Secondary efficacy analyses were performed at Weeks 12 and 24. This trial was well-controlled and had endpoints that are considered acceptable for efficacy evaluations in AS.

In the pre-specified primary analyses, certolizumab met the primary and key secondary endpoints. Baseline data suggest important genetic and demographic differences between the AS and nr-axSpA subgroups within the broader axial SpA population. Further, functional impairment, disease activity, and objective markers of inflammation appeared to differ for these subgroups. Given the heterogeneity of axial SpA, it was unclear if the magnitude of the treatment effect was similar in these subgroups. In trial AS001, patients were classified into the subgroups AS and nr-axSpA based on the presence or absence of radiographic changes consistent with AS on sacroiliac x-rays at screening. There appeared to be limitations in defining these subgroups based on x-rays given differences in interpretation of sacroiliac x-rays depending on whether the x-rays were evaluated locally or centrally. The differences in classification were especially notable for patients with nr-axSpA.

In order to evaluate if the effect of treatment varied substantially across important subgroups, the Sponsor stratified by these subgroups and evaluated for consistency across the subgroups. Subgroup classification was either by central or local x-ray interpretation. In general, the trends seen in the subgroups were consistent with those demonstrated in the overall population. The magnitude of effect in the subgroups did vary for some endpoints when the subgroup assignment was determined by local or central x-ray assessments. It is important to recognize that certolizumab is not currently approved for the treatment of AS.

We recognize that these subgroup analyses are exploratory and should be interpreted

cautiously. In general, the best test of validity in subgroup analyses is not significance, but independent substantiation of results. Further, based on central x-ray classification, the majority of patients had AS, and it was unclear if the results could be extrapolated to the broad population of active axial SpA.

Summary of Safety

The safety information for certolizumab in axial SpA is obtained from one trial during which 274 patients received at least one dose of certolizumab. The Sponsor submitted data from the 24-week double-blind period. The median treatment duration was 20 weeks (range 4 to 25 weeks). Following the 24-week double-blind period, there was an ongoing 110-week open label extension. However, the primary safety analyses are derived from the completed 24-week double-blind treatment period.

There were no deaths during the 24-week, double-blind treatment period.

Serious adverse events (SAEs) were uncommon during the 24-week, double-blind treatment period. The proportion of patients with SAEs was balanced between the overall certolizumab group and the placebo group (5% for each). No SAEs were reported in more than one patient. A slightly higher percentage of patients treated with certolizumab 400mg Q4W had SAEs compared to the placebo and certolizumab 200mg Q2W groups. The percentage of patients with SAEs in the system organ class (SOC) hepatobiliary disorders and infections and infestations was slightly higher in the patients treated with certolizumab than placebo.

The proportion of patients with adverse events (AEs) leading to discontinuation was balanced between the placebo and certolizumab groups. A slightly higher proportion of patients in the certolizumab group compared to the placebo group had AEs. The most common AEs in the certolizumab-treatment group were nasopharyngitis (9%), headache (6%), blood creatine phosphokinase increased (5%), and rash (4%). All of these AEs were more common in the certolizumab-treatment group than the placebo-treatment group, except for headache.

Due to specific safety concerns with TNF-inhibitors, analyses were conducted related to AEs of special interest, including infections, malignancies, hepatotoxicity, cardiovascular events, demyelinating disorders, injection site reactions, autoimmunity, and hematologic cytopenias. These analyses did not reveal new safety concerns with the use of certolizumab in axial SpA.

Overall, no new safety signals were identified in Trial AS001 and certolizumab had a similar safety profile in axial SpA compared to the safety profile reflected in the product label. While no new safety signals were identified in Trial AS001, the safety profile of certolizumab is well-characterized for RA patients and the known risks of certolizumab should be considered in the risk/benefit consideration.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A REMS is not recommended because no new safety issues were identified in this submission.

1.4 Recommendations for Postmarket Requirements and Commitments

Studies to achieve compliance with PREA
The juvenile equivalents of AS are extremely rare. The Sponsor has submitted a full waiver request for pediatric patients under the age of 18 years with axial SpA. The Sponsor's justification is based on the argument that studies would be impossible or impractical due to the uncommon occurrence of axial SpA and inflammatory back pain in children. The most widely accepted classification system used in children with inflammatory arthritis at the current time is the International League of Associations of Rheumatology (ILAR) classification system for juvenile idiopathic arthritis (JIA). This classification system defines seven discrete categories of arthritis starting before the age of 16 years. None of the seven categories represent a pediatric form of axial SpA.

Currently, there are no epidemiologic data of axial SpA patients with symptom onset under age 18 years who fulfill the ASAS classification criteria for axial SpA. In addition, there are limited epidemiologic data available for patients under 18 years who fulfill the modified New York criteria for AS. The prevalence of juvenile AS is estimated to be about 12 to 33 per 100,000 children in England and in the United States[13]. Based on the limited data for juvenile AS in the US showing relatively low disease prevalence, the lack of classification criteria specifically validated for axial SpA in the pediatric population and the difference in clinical presentation from adults, the sponsor requests a waiver for pediatric axial SpA patients under the age of 18. Previously, the Agency has waived studies in pediatric AS due to similar rationale.

2 Introduction and Regulatory Background

2.1 Product Information

Proposed Trade Name (established name): Cimzia® (certolizumab)

Proposed Indication: The proposed indication in the submitted label is "treatment of adult patients with active axial spondyloarthritis, including patients with ankylosing spondylitis." Following the Advisory Committee Meeting on July 23, 2013, the Sponsor proposed the following indication in a submission dated August 9, 2013: "treatment of

(b) (4)

(b) (4)

Proposed Age Group: Adult patients

Proposed Dose Regimen: 400mg (given as 2 subcutaneous [SC] injections of 200mg each) initially and at weeks 2 and 4, followed by 200mg SC every 2 weeks or 400mg every SC 4 weeks.

Pharmacological Class: Monoclonal antibody Fab' fragment to TNF-alpha

Description: Certolizumab is a recombinant, humanized monoclonal antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNF-alpha), conjugated to an approximately 40kDa polyethylene glycol (PEG2MAL40K). The Fab' fragment is produced by *Escherichia coli*.

How supplied: Certolizumab is supplied as a sterile solution for subcutaneous injection and a sterile, lyophilized powder for reconstitution and then subcutaneous administration. The drug product is supplied as either a single-use, 1 mL prefilled glass syringe or a single-use, vial containing approximately 200mg of certolizumab.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no approved products in the United States to treat axial SpA. However, there are approved products to treat AS, which is a subset of the broader axial SpA indication. Specifically, there are four biologic TNF-inhibitors that are approved in the United States for the treatment of AS (Table 3).

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Table 3: Approved products for the treatment of AS in the United States†

	Product	BLA (Sponsor)	Date of approval for AS‡	Characteristic	ROA
1	Etanercept (Enbrel®)	103795 (Immunex)	7/24/03	Fusion protein (TNF-inhibitor)	SC
2	Infliximab (Remicade®)	103772 (Centocor)	12/17/04	Monoclonal antibody (TNF-inhibitor)	IV
3	Adalimumab (Humira®)	125057 (Abbott)	8/28/06	Monoclonal antibody (TNF-inhibitor)	SC
4	Golimumab (Simponi®)	125289 (Centocor)	4/24/09	Monoclonal antibody (TNF-inhibitor)	SC

Abbreviations: BLA=Biologics License Applications; ROA=route of administration; SC=subcutaneous; IV=intravenous; RA=rheumatoid arthritis; PsA=psoriatic arthritis; AS=ankylosing spondylitis
† NSAIDs (e.g., celecoxib, diclofenac, indomethacin, naproxen, sulindac) and steroids (e.g., betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone) are also approved for the treatment of AS
‡ Etanercept was originally approved in 1998 for RA, infliximab was originally approved in 1998 for Crohn's Disease, adalimumab was originally approved in 2002 for RA, and golimumab was approved for RA, PsA, and AS concurrently
Source: FDA generated from prescribing information for infliximab, etanercept, adalimumab, golimumab (accessed May 20, 2013)

2.3 Availability of Proposed Active Ingredient in the United States

Certolizumab is commercially available in the United States. Certolizumab received FDA approval on April 22, 2008 for the treatment of Crohn's disease. It was subsequently approved for the treatment of RA.

2.4 Important Safety Issues with Consideration to Related Drugs

There are five biologic TNF-inhibitors that are approved in the United States (see Table 4) for multiple inflammatory diseases in adults (RA, PsA, AS, psoriasis [Ps], CD, and ulcerative colitis [UC]) and two pediatric diseases (pediatric CD and juvenile idiopathic arthritis [pJIA]). Of the five approved biologic TNF-inhibitors, four are approved for AS. Certolizumab is not currently approved for the treatment of AS.

Table 4: Approved biologic TNF-inhibitors in the United States as of May 30, 2013†

	Product	BLA (Sponsor)	Year of initial approval	Characteristic	ROA	Approved indications	Proposed indications
1	Etanercept (Enbrel®)	103795 (Immunex)	1998	Fusion protein (TNF-inhibitor)	SC	RA, PsA, AS, Ps, pJIA	N/A
2	Infliximab (Remicade®)	103772 (Centocor)	1998	Monoclonal antibody (TNF-inhibitor)	IV	RA, PsA, AS, Ps, CD, pediatric CD, UC, pediatric UC	N/A
3	Golimumab (Simponi®)	125289 (Centocor)	2009	Monoclonal antibody (TNF-inhibitor)	SC	RA, PsA, AS	N/A
4	Certolizumab (Cimzia®)	125160 (UCB)	2008	Fab fragment (TNF-inhibitor)	SC	RA, CD	Axial SpA†
5	Adalimumab (Humira®)	125057 (Abbott)	2002	Monoclonal antibody (TNF-inhibitor)	SC	RA, PsA, AS, Ps, CD,UC, pJIA	Nr-axSpA†

† supplemental BLA under review
Abbreviations: BLA=Biologics License Applications; ROA=route of administration; SC=subcutaneous; IV=intravenous; RA=rheumatoid arthritis; PsA=psoriatic arthritis; AS=ankylosing spondylitis; Ps=psoriasis; CD=Crohn's disease; pJIA=polyarticular juvenile idiopathic arthritis; UC=ulcerative colitis; nr-axSpA=non-radiographic axial spondyloarthritis
Source: FDA generated from prescribing information for infliximab, etanercept, adalimumab, golimumab, certolizumab (accessed May 20, 2013)

Table 5 displays adverse reactions that have been associated with the use of TNF-inhibitors and appear in the Boxed Warnings and Warnings and Precautions section of at least one biologic TNF-inhibitor product label. See Section 7.3.5 (Submission Specific Primary Safety Concerns) for an evaluation of the association of certolizumab with these known TNF-inhibitor adverse events.

Table 5: Overview of safety concerns with TNF-inhibitors

Location in label†	Safety concerns
Boxed Warnings	1. **Serious infections,** including bacterial sepsis, tuberculosis, invasive fungal infections, histoplasmosis, and other opportunistic infections 2. **Malignancies**, including hepatosplenic T-cell lymphoma, lymphoma, and other malignancies in children and adolescents
Warnings/Precautions	1. Infections 2. Hepatitis B reactivation 3. Invasive fungal infections 4. Malignancies 5. Hepatoxicity 6. Hypersensitivity disorders 7. Demyelinating disorders (e.g., multiple sclerosis) 8. Adverse outcomes in patients with heart failure 9. Pancytopenia, leukopenia, neutropenia, thrombocytopenia 10. Autoimmune disorders (e.g., lupus-like syndrome) 11. Infusion-related reactions/Injection-site reactions

† All TNF-inhibitor labels do not contain all of these safety concerns
Source: FDA generated from prescribing information for infliximab, etanercept, adalimumab, golimumab , certolizumab(accessed May 20, 2013)

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

An overview of the important regulatory interactions pertaining to the current submission is shown in Table 6. In 2010, the Sponsor proposed a trial in patients with axial SpA to support a broader indication than AS. The Sponsor proposed to study the efficacy of certolizumab in patients who met the imaging definition of the ASAS criteria or the classical modified NY diagnostic criteria. Thus, the Sponsor proposed to include patients with x-ray or MRI evidence of sacroiliitis, but exclude patients who only met the ASAS clinical criteria for axial SpA. Subsequently, the Sponsor amended the protocol to remove the exclusion of patients who only met the ASAS clinical criteria for axial SpA. At that time of the initial proposal, the FDA expressed that it might be reasonable to trial a broader population of patients with axial SpA. Subsequently, when the Sponsor had a pre-sBLA meeting with the FDA in 2012, regulatory concerns were raised regarding use of the imaging and clinical ASAS classification criteria to define a patient population that would be the basis of a new indication. Specific concerns included the lack of clarity in the entities the criteria would encompass and whether patients would evolve into other diagnoses for which treatment may have an unfavorable or unknown risk/benefit profile. The FDA noted that a discussion of the regulatory implications of the new ASAS classification criteria would likely occur in a public forum, such as an advisory committee meeting.

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Table 6: Overview of regulatory interactions for the axial spondyloarthritis development program

Meeting Date	Type of Meeting	FDA recommendations and key discussion topics
2/9/10	EOP2 Meeting	1. The Sponsor proposed 1 trial in axial SpA to support the indication "axial spondyloarthritis". The proposed trial was a randomized, double blind, placebo controlled trial with a primary endpoint at 12 weeks. Patients met the ASAS criteria and had sacroiliitis documented by x-ray or MRI. These patients were described as early or late AS. 2. FDA indicated that it would be generally acceptable to use the ASAS classification criteria to select a broader population of patients with axial SpA, which would include early AS. Of note, the Sponsor's description of the ASAS classification criteria is slightly different than the actual criteria. The Sponsor proposed to include patients only if they had evidence of sacroiliitis on x-ray or MRI.
7/31/12	Pre-sBLA meeting	1. FDA raised regulatory concerns regarding the use of the new ASAS axial SpA classification criteria to define a new indication. Specifically, there was concerns regarding the lack of clarity of the entities the criteria would encompass and whether patients could evolve into other diagnoses for which treatment may have an unfavorable or unknown risk/benefit profile. 2. Discussion of the proposed indication would likely occur in a public forum, such as an advisory committee meeting

Abbreviations: SpA=spondyloarthritis; FDA=Food and Drug Administration; ASAS=Assessment of Spondyloarthritis international Society; EOP2=end of phase 2; sBLA=supplemental biologic license application
Source: FDA generated

Reviewer's comments: When the Sponsor originally proposed in 2010 to consider expanding the population studied from AS to patients without radiographic changes consistent with AS, they proposed to only include patients with MRI or x-ray findings consistent with AS. Whether or not the risk/benefit assessment of certolizumab is affected by inclusion of patients who lack evidence of sacroiliitis on imaging is unclear.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

The electronic sBLA submission was well-organized and complete and there were no major amendments.

3.2 Compliance with Good Clinical Practices

According to the Sponsor, study AS001 was conducted in compliance with good clinical practice (GCP) guidelines, as described in the 1996 International Committee on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP, U.S. Code of Federal Regulations (CFS) dealing with clinical studies, informed consent, and institutional review board (IRB) regulations, the European Union Directive, the Declaration of Helsinki concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects), and other applicable local/regional regulations and guidelines regarding the conduct of clinical studies. A signed informed consent form was obtained from each patient prior to enrollment and IRB approval was obtained by the investigators.

As certolizumab is an approved product and there were no concerns regarding compliance with good clinical practice, the Office of Scientific Investigation was not requested to perform routine audits of clinical sites.

3.3 Financial Disclosures

The Sponsor submitted FDA Form 3454 certifying that the Applicant did not enter into any financial arrangement with the clinical investigators in the certolizumab studies whereby the value of compensation to the investigators could be affected by the outcome of the study as defined in 21 CFR 54.2(a). In addition, the Sponsor certified that each clinical investigator was required to disclose to the Sponsor whether the investigator had proprietary interest in certolizumab or a significant equity interest in the Sponsor as defined in 21 CFR 52.2(b). Finally, the Sponsor certified that no listed investigator was the recipient of significant payments as defined in 21 CFR 54.2(f). No potentially conflicting financial interests were identified.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new chemistry manufacturing and controls data were submitted with this supplement for review.

4.2 Clinical Microbiology

No new clinical microbiology data were submitted with this supplement for review.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical pharmacology/toxicology data were submitted with this supplement

for review.

4.4 Pharmacokinetics

4.4.1 Mechanism of Action

No new data on the mechanism of action were submitted with the current supplement for review. Certolizumab binds specifically to TNF-alpha, which is a pro-inflammatory cytokine with a central role in inflammatory processes. Certolizumab has been previously shown to neutralize membrane-associated and soluble human TNFα in a dose-dependent manner.

4.4.2 Pharmacodynamics

No new pharmacodynamic data were submitted with the current supplement for review.

4.4.3 Pharmacokinetics

No new pharmacokinetic data were submitted with the current supplement for review.

During the 24-week double blind portion of the study, all doses of investigational product were administered by unblinded site staff. Self-administration began at week 26. During the self-administration portion of the study, patients were trained by the site staff and provided written instructions on the correct sc injection technique. Patients self-administered their initial injections at Weeks 26 and 28 under supervision of the site staff to ensure that the study medication was being properly and safely injected. Suitable areas for self-injection were the lateral abdominal wall and upper outer thigh. Once trained, during self-administration-weeks, patients could self-inject their study medication at home. Patients who were unable to self-administer the study treatment or those without a family member/friend/caregiver who could help, were not to be discontinued but could continue to visit the site for study treatment administration.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Sponsor submitted the following data from one completed trial of certolizumab in their sBLA to support the approval of certolizumab for the treatment of axial spondyloarthritis:

- One randomized, double-blind, parallel-group, placebo-controlled trial (AS001, see Table 7). The Sponsor submitted data to Week 24.

Table 7: Overview of randomized, placebo-controlled trial in axial spondyloarthritis

Trial	Design/ Sites	Patient population	Treatment	N†	Primary efficacy variable
AS001	R, DB, PC, PG trial/ 128 sites	Active axial spondyloarthritis with an inadequate response to NSAIDs or a contraindication to NSAIDs	**24-week controlled period‡:** • CZP 400mg at weeks 0, 2, and 4 followed by CZP 200mg q2w • CZP 400mg at weeks 0, 2, and 4 followed by CZP 400mg q2w • Placebo **110-week open label extension:** • CZP 200mg q2w • CZP 400mg q4w	111 (CZP 200mg q2w 107 (CZP 400mg q4w) 107 (placebo)	ASAS20 at week 12

†=Number of patients randomized; ‡=escape treatment was given to placebo patients who did not achieve a minimal response at both Weeks 14 and 16
Abbreviations: R=randomized; DB=double blind; PC=placebo controlled; PG=parallel group; CZP=certolizumab, q2w=every 2 weeks, q4w=every 4 weeks
Source: Adapted from Tabular listing of all clinical studies (Module 5.2), received 12/14/12, page 1

5.2 Review Strategy

Efficacy: Trial AS001 served as the one phase 3 trial for the evaluation of the efficacy of certolizumab in the treatment of signs and symptoms of axial spondyloarthritis (axial SpA). This trial was well-controlled and had endpoints that are considered acceptable for efficacy evaluation in AS. It is unclear whether the trial design and endpoints are reasonable for patients with axial SpA. The trial included two subgroups of patients: AS and nr-axSpA. Of note, classification into these subgroups varied depending on whether x-rays were evaluated by local investigators or central assessors. The efficacy and safety results in the trial were evaluated in the overall population and the two subgroups. All patients had active disease defined as a BASDAI score≥4, spinal pain ≥4 on a 0 to 10 numerical rating scale (NRS), and CRP >ULN and/or current evidence of sacroiliitis on MRI as defined by the ASAS criteria.

Safety: The major safety evaluation of certolizumab for the treatment of signs and symptoms of axial SpA was Trial AS001. The primary safety analyses focused on data through Week 24—the double-blind, placebo-controlled period. For the Week 24 analyses, the treatment groups included the treatment groups assigned at randomization and the group of patients who received certolizumab at any time during the 24-week trial (all certolizumab group). Patients in the placebo group with ongoing disease activity escaped to certolizumab treatment at week 16. These patients who escaped from placebo to certolizumab were considered in the all certolizumab group.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Trial AS001

The following description of the protocol for Trial AS001 is based on amendment 4 of the protocol (dated April 27, 2011) and the statistical analysis plan (dated March 22, 2012). See Table 8 for the dates and description of all amendments to the protocol for Trial AS001.

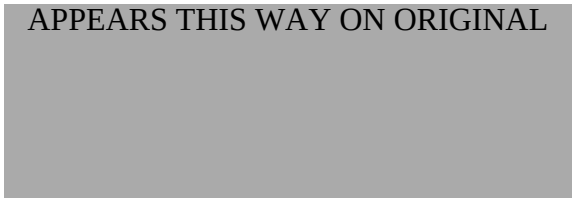

Table 8: Overview of protocol amendments to trial AS001

Amendment	Date	Major modifications
Original Protocol	September 25, 2009	• Not applicable
Amendment 1	November 23, 2009	• Inclusion criteria broadened to include patients meeting the ASAS clinical criteria and not limited only to patients meeting the new ASAS imaging criteria • Patients meeting the new imaging criteria represented at least 50% of patients not meeting the modified NY criteria • Clarification was included that x-rays and MRI documenting sacroiliitis for patients meeting the new ASAS imaging criteria must be read by a radiologist (MRI) and records (x-rays and MRIs) must be included in source documentation • Updates made to Exclusion Criteria 6 and 7 to more clearly define exclusion of patients with fibromyalgia • Secondary objective statement added, including secondary (Patient Acceptable Symptomatic Scale and Physician Acceptable Symptomatic State) and exploratory (Patient's Global Impression of Change [PGIC]) variables • Required sacroiliac joint x-ray at Baseline for all patients not receiving a baseline MRI • Added possible use of other MRI reading criteria, such as Berlin or modified Berlin criteria • Clarification added that the 44 joint counts included both swollen AND tender joint counts • Clarification added that recording the axial SpA history includes relevant family history and prior and concomitant medication history
Amendment 2	March 15, 2010	• Adjusted the statistical analysis plan for multiple endpoints and to change to the Randomized Set for primary efficacy analyses • A CRP greater than upper limit of normal was added to inclusion criteria #6. One retesting of patients failing screening due to CRP level was permitted. • Clarification added that sacroiliac joint x-rays were performed at Baseline for **all** patients • Sacroiliac joint x-rays performed **<12 weeks** (instead of <4 weeks) prior to the Baseline Visit may be used as the Baseline assessment provided the film can be submitted and meets the requirements for central reading • Clarification added that patients enrolled on the basis of meeting the imaging criteria needed to have been on this basis prior to the Screening Visit • The statement requiring x-ray or MRI documenting sacroiliitis within 6 months of Screening was removed • Clarification added that in addition to the modified

		Stokes Ankylosing Spondylitis Spine Score (mSASSS), x-rays could be evaluated using other assessments • Clarification was added that subjects meeting the definite AS diagnosis according to the modified NY criteria were defined as subjects meeting NY criteria • Clarification on the definition of inflammatory back pain for axial SpA was added
Amendment 3	December 6, 2010	• Inclusion Criterion #5 was clarified to ensure that the symptom duration of adult-onset axial SpA was at least 3 months and to reduce confusion about the requirements of the trial population • Inclusion Criterion #6 was expanded to include patients with MRI evidence of sacroiliitis
Amendment 4	April 27, 2011	• MRI was added at Week 48 • The spine MRI scoring system was changed from SPARCC scores to AS spine MRI scoring system for disease activity (ASspiMRI-a) in the Berlin modification
Other changes to trial conduct		• Although Protocol Amendment 1 specified that x-rays and MRIs documenting sacroiliitis were to be read by a radiologist, both rheumatologists and radiologists reviewed x-rays and MRIs • The MRI scoring method used in AS001 did not permit assessment of structural damage. Rather, this was assessed with spinal x-rays in the MRI sub-study.

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Title: Trial AS001 is entitled, "Phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety of certolizumab pegol in subjects with axial spondyloarthritis (Axial SpA)."

Trial Dates: April 9, 2010 through trial visit week 24 for all subjects as of January 14, 2012

Sites: 128 sites located in North America, Latin America, Western Europe, and Central/Eastern Europe

Objectives of Trial AS001: The primary objective of the trial was to demonstrate the efficacy of certolizumab administered subcutaneously (SC) at the doses of 200mg every 2 weeks (Q2W) and 400mg every 4 weeks (Q4W) after a loading dose of 400mg at weeks 0, 2, and 4 on the signs and symptoms of active axial spondyloarthritis (axial SpA).

The secondary objectives of the trial were to assess the effects on safety and tolerability and to demonstrate the effects of certolizumab on health outcomes, partial remission, spinal mobility, and structural damage and inflammation in the subpopulation of patients with MRIs. The other objectives were to assess the effect of certolizumab on enthesitis, direct medical resource utilization, subject's health status, structural damage in the subpopulation of subjects with x-rays, and assessment of subject symptomatic state.

Overall Design of Trial AS001: Trial AS001 was a multicenter, randomized, double-blind, placebo-controlled trial of certolizumab in adult patients with active axial SpA. The trial included 5 periods:

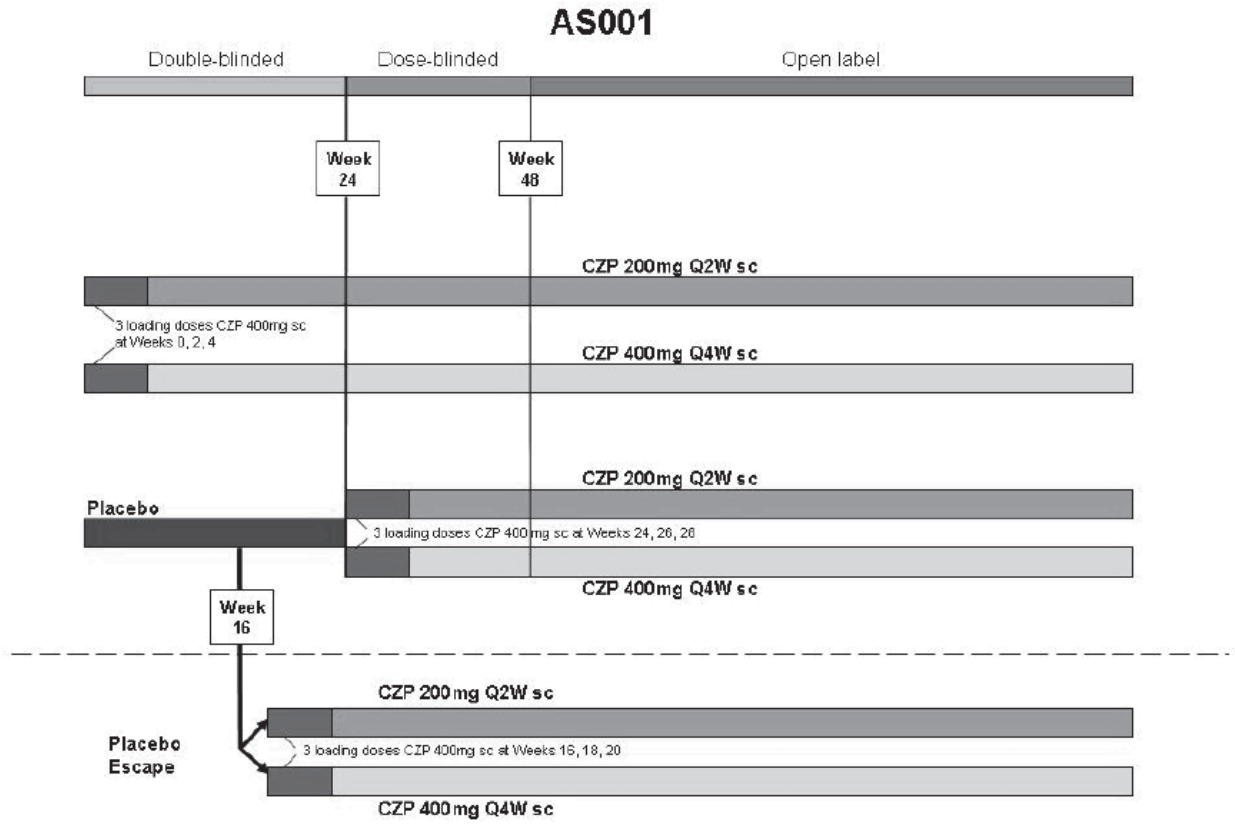
- Period 1: Screening period of 1 to 5 weeks
- Period 2: Double-blind, placebo-controlled period (Week 0-24)
    i. Eligible patients were randomized to the following trial treatments in a 1:1:1 ratio:
        1. Certolizumab administered SC at a dose of 400mg Q2W at Weeks 0, 2, and 4 followed by 200mg Q2W SC (starting at Week 6)
        2. Certolizumab administered SC at a dose of 400mg Q2W at Weeks 0, 2, and 4 followed by 400mg Q4W SC (starting at Week 8)
        3. Placebo

- Period 3: All patients received treatment with certolizumab, but were blinded to the dose (Weeks 24-48). All patients were trained on self-administration at Weeks 26 and 28. Patients had the option of self-administering 1 injection at home Q4W starting from Week 30.

- Period 4: All patients continued to receive the same dose regimen of certolizumab they received during Period 3. After Week 48, only patients randomized to certolizumab 200mg Q2W self-administered trial treatment Q4W at home. All other injections were self-administered (preferably), during scheduled visits.
- Period 5: All patients, including those withdrawn from trial treatment, had safety follow-up visits 10 weeks after their last dose of trial medication.

Escape treatment: Patients receiving placebo who did not achieve at least a minimal response (defined as an ASAS20 response at both Weeks 14 and 16) were allocated to escape treatment (randomized in a 1:1 ratio to receive certolizumab 200mg Q2W or certolizumab 400mg Q4W from Week 16 onwards).

Figure 1: Trial AS001 schematic



Source: Study AS001 Complete Study Report (Module 5.3.5.1.2), received 12/14/12, page 51

Patient Selection for Trial AS001:

Trial AS001 randomized 325 patients who met the following inclusion and exclusion criteria:

Inclusion criteria:

To be eligible to participate in the trial, patients had to have met all of the following criteria:

1. Patients at least 18 years old at the Screening Visit
2. An IRB/IEC-approved written informed consent was signed and dated by the patient
3. The subject was considered reliable, willing and capable of adhering to the protocol, visit schedule, and medication intake according to the judgment of the Investigator
4. Female patients had to be either postmenopausal for at least 1 year, surgically incapable of childbearing, or effectively practicing an acceptable method of contraception (oral/parenteral/implantable hormonal contraceptives, intrauterine device or barrier and spermicide). Abstinence only was not an acceptable method. Subjects had to agree to use adequate contraception during the trial and for at least 10 weeks (or longer if required by local regulations) after the last dose of trial treatment. Male subjects had to agree to ensure they or their female partner(s) used adequate contraception during the trial and for at least 10 weeks (or longer if required by local regulations) after the subject received their last dose of trial treatment.
5. Patients had to have a documented diagnosis of adult-onset axial SpA of at least 3 months symptom duration as defined by the specified ASAS criteria (see Table 9).
    - 50% of the trial population who met the ASAS criteria should NOT have fulfilled the modified NY criteria for definite diagnosis of AS.
    - In order to fulfill the imaging criteria, MRIs had to be read by a radiologist and x-ray and MRI reports had to be included in source documentation.
    - Of the remaining 50% of the trial population, at least 50% (25% of the total trial population) had to meet the ASAS imagining criteria. The remaining 50% of patients could be enrolled based on the ASAS clinical criteria only.
6. Patients had to have **active disease** as defined by each of the following:
    - BASDAI score ≥4
    - Spinal pain ≥4 on a 0 to 10 Numerical Rating Scale (NRS) (from BASDAI item 2)
    - CRP>ULN and/or current evidence (ie, within the last 3 months from Screening) of sacroiliitis on MRI as defined by ASAS criteria (see Table 9)
7. Patients had to have been intolerant to or have had an inadequate response to at least 1 NSAID. Inadequate response to an NSAID was defined as lack of response to at least 30 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID or the lack of response to treatment with at least 2 NSAIDs at the maximum tolerated dose for 2 weeks each.

Table 9: ASAS classification criteria for axial SpA

(for subjects with chronic back pain ≥3 months and age at onset <45 years)

Imaging criteria	ASAS clinical criteria for axial SpA
Sacroiliitis (MRI or radiographs*) plus ≥1 SpA feature	HLA-B27 plus ≥2 other SpA features
SpA features**	
Inflammatory back pain***	Psoriasis
Arthritis	Crohn's disease/ulcerative colitis
Enthesitis (heel)	HLA-B27
Uveitis	Elevated CRP
Dactylitis	

CRP=C-reactive protein; MRI=magnetic resonance imaging; HLA-B27=human leukocyte antigen B27; NSAID=nonsteroidal anti-inflammatory drug; SpA=spondyloarthritis

* Active inflammatory lesions of sacroiliac joints with definite bone marrow oedema/osteitis suggestive of sacroiliitis associated with spondyloarthritis in MRI or radiographic sacroiliitis grade 2 to 4 bilaterally or grade 3 to 4 unilaterally according to modified NY criteria.

** Family history for SpA and Good response to NSAIDs are excluded as SpA feature criteria.

***Inflammatory back pain according to ASAS criteria for Axial SpA defined as the presence of 4 out of 5 of the following parameters:

1) age at onset <40 years
2) insidious onset
3) improvement with exercise
4) no improvement with rest
5) pain at night (with improvement upon getting up)

Source: Study AS001 Complete Study Report (Module 5.3.5.1.2), received 12/14/12, Table 17.2, page 91

Reviewer's comments: An important feature of the inclusion criteria is the requirement for active disease, which is defined as a BASDAI score ≥4, spinal pain ≥4, and CRP>ULN or MRI with evidence of inflammation according to the ASAS criteria. Also, it is important to note that the ASAS classification criteria were modified as family history of SpA and good response to NSAIDs were excluded as SpA feature criteria.

Exclusion Criteria:

Subjects were not permitted to enroll in the trial if any of the following criteria were met:

1. The patient had previously participated in this trial or had previously received certolizumab treatment in or outside of another clinical trial
2. The patient had participated in another trial of a medication or a medical device under investigation within the prior 3 months or was currently participating in another trial of a medication or medical device under investigation
3. Patient had a history of chronic alcohol abuse (more than 14 drinks/units per week for women and 21 drinks/units for men [1 drink=4oz of wine, 12oz of beer, or 1oz of hard

liquor] or 330mL of 5% alcohol by volume beer=2 units, 125mL of 12% wine=1.5 units, 50mL of 40% spirits=2 units) or drug abuse within the last year
4. Patient had any medical or psychiatric condition (according to the Diagnostic and Statistical Manual of Mental Disorders criteria) that, in the opinion of the Investigator, could have jeopardized or compromised the subject's ability to participate in this trial
5. Patient had a known hypersensitivity to any components of certolizumab, placebo, or with a history of an adverse reaction to PEG

Axial spondyloarthritis disease-related exclusions
6. Patients must not have had total spinal ankylosis ("bamboo spine"), a diagnosis of any other inflammatory arthritis (e.g., RA, systemic lupus erythematosus, sarcoidosis) or a known diagnosis of fibromyalgia.
7. Patients must not have had a secondary, noninflammatory condition (e.g., osteoarthritis) that in the Investigator's opinion was symptomatic enough to interfere with evaluation of the effect of trial drug on the subject's primary diagnosis of axial SpA.

Prior medication exclusions:
8. Patients must not have used the following medications in the manner as detailed by the exclusion criteria in Table 10. No more than 40% of subjects were to be secondary failures to anti-TNF-alpha.

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Table 10: Prior medication exclusions

Drug class	Dose	Exclusion criteria
Analgesics (acetaminophen, etc)	Any dose	Any ad hoc use in the 24 hours prior to the baseline visit. Stable doses of analgesics permitted.
NSAIDs/cyclooxygenase-2 (COX-2) inhibitors	Any dose regimen	Any change in dose regimen in the 14 days prior to the Baseline visit
Oral corticosteroids	Maximum allowed ≤10mg daily total prednisone equivalent	Any change in dose in the 28 days prior to the Baseline Visit
Intramuscular (im)/intravenous (iv)/intra-articular (ia) corticosteroids	Any dose	Use in the 28 days prior to the Baseline Visit
Intra-articular hylauronic acid	Any dose	Use in the 28 days prior to the Baseline Visit
sDMARDs: sulfasalazine (SSZ) and/or hydroxychloroquine (HCQ) and/or methotrexate (MTX)	Maximum allowed: SSZ≤3g daily HCQ≤400mg daily MTX≤25mg weekly	Use initiated and or any change in the dose regimen in the 28 days prior to the Baseline Visit. No change is permitted in the route of administration for MTX (im, sc, or oral) in the 28 days prior to the Baseline Visit.
sDMARDs: azathioprine, cyclosporine, cyclophosphamide, mycophenolic acid	Any dose	Use within 28 days prior to the Baseline Visit.
sDMARDs: leflunomide	Any dose	Use in the 6 months prior to the Baseline Visit unless a cholestyramine washout has been performed; in which case, use 28 days prior to the Baseline Visit is acceptable.
Biologics: infliximab (IFX), adalimumab (ADA), etanercept (ETN), golimumab (GOL), abatacept (ABA)	Any dose	For IFX, ADA, GOL, and ABA any use within the 3 months prior to the Baseline Visit. For ETN, use within 28 days prior to the Baseline Visit.
Other biologics: anti-CD20, tocilizumab, certolizumab	Any dose	Any exposure history

Abbreviations: ABA=abatacept; ADA=adalimumab; COX-2=cyclo-oxygenase-2; sDMARD=synthetic disease modifying antirheumatic drug; ETN=etanercept; GOL=golimumab; HCQ=hydrochychloroquine; IFX=infliximab; iv=intravenous; im=intramuscular; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; SSZ=sulfasalazine
Source: Study AS001 Complete Study Report (Module 5.3.5.1.2), received 12/14/12, Table 3-1, pages 32-33

Previous clinical studies and previous biological therapy exclusions

9. Patients must not have received any nonbiological therapy for axial SpA not listed above within or outside a clinical trial in the 3 months or within 5 half-lives prior to the Baseline Visit (whichever was longer).
10. Patients must not have received any experimental biological agents other than those permitted in Table 10 (defined as those agents unlicensed for use in axial SpA in Europe or the USA).
11. Patients must not have received previous treatment with a PEGylated compound that resulted in a severe hypersensitivity reaction or an anaphylactic reaction.

12. Patients must not have been exposed to more than 1 anti-TNF-alpha prior to the Baseline Visit and must not have been a primary failure to any anti-TNF-alpha therapy (defined as no response within the first 12 weeks of treatment with the anti-TNF-alpha).
13. Patients must not have been exposed to more than 2 previous biological agents for axial SpA.

Medical history exclusion:

14. Female patients who were breastfeeding, pregnant or planned to become pregnant during the trial or within 3 months following the last dose of the investigational product.
15. Subjects with a history of chronic or recurrent infections (more than 3 episodes requiring antibiotics or antivirals during the preceding year), recent serious or life–threatening infection within the 6 months prior to the Baseline Visit (including herpes zoster), hospitalization for any infection in the last 6 months or any current sign or symptom that could have indicated an infection.
16. Known TB disease, high risk of acquiring TB infection, or latent TB infection:

a. Known TB disease
◦ Currently active TB disease or clinical signs and symptoms suspicious for TB.
◦ Prior history of active TB disease involving any organ system (clinically documented).
◦ Chest radiograph evidence of past active TB disease (not clinically documented), which could have included apical lung fibrosis, pleural thickening, calcified lung nodules, calcified hilar lymph nodes, pericardial calcification.
b. High risk of acquiring TB infection
◦ Known exposure to another person with active TB disease <3 months prior to Screening.
◦ High risk of future exposure to another person with active TB disease:
1. Time spent in a health care delivery setting.
2. Time spent in an institutional setting.
c. Latent TB infection - Subjects who didn't meet criteria "a" or "b" but met any of the following, regardless of prior TB treatment:
◦ Current PPD positive (+) (test had to have been performed ≤3 months prior to Screening)
or
◦ Previously documented history of a severe positive PPD reaction (test performed >3 months prior to Screening) and
1. Elispot (performed ≤3 months prior to Screening) positive or indeterminate
or
2. QuantiFERON (performed ≤3 months prior to Screening, only if Elispot unavailable) positive or indeterminate.

- Patients with no documented history of a severe positive PPD test could only receive the PPD test for Screening.
- Exception from exclusion "c" was permitted only if treatment for latent TB infection was initiated or had been initiated at least 4 weeks prior to trial drug administration and treatment was still ongoing at time of trial entry.

- A positive PPD was defined as ≥5mm of induration 48 to 72 hours after intradermal injection of 5 Tuberculin Units (TU) of PPD-S or 2TU of PPD-RT23 regardless of the subject's history of BCG vaccination.
- Reports of PPD results not taken at Screening but (performed ≤3 months prior to Screening and) reported from elsewhere must have been documented with exact induration measurement.
- Treatment for latent TB infection included, e.g., isonicotinic acid hydrazide/isoniazid (INH) therapy for 9 months (with vitamin B6); another latent TB infection treatment regimen should have been considered if the subject was living in or had emigrated recently from a country with a high endemic rate of INH-resistant or multi-drug resistant TB

17. Patients with concurrent acute or chronic viral hepatitis B or C or with known human immunodeficiency virus (HIV) infection.
18. Patients with known history of or current clinically active infection with *Histoplasma*, *Coccidiodes*, *Paracoccidioides*, *Pneumocystis*, nontuberculous mycobacteria, *Blastomyces*, or *Aspergillus*.
19. Patients must not have had a history of an infected joint prosthesis at any time with that prosthesis still in situ.
20. Patients receiving any live (includes attenuated) vaccination within the 8 weeks prior to Baseline (e.g., inactivated influenza and pneumococcal vaccines were allowed but nasal influenza vaccination was not permitted).
21. Patients with a high risk of infection in the Investigator's opinion (e.g., subjects with leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections and subjects who were permanently bedridden or wheelchair bound).
22. Patients with a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.
23. Concurrent malignancy or a history of malignancy (subjects with less than 3 excised basal cell carcinomas or with cervical carcinoma in situ successfully surgically treated more than 5 years prior to Screening could have been included).
24. Patients with Class III or IV congestive heart failure as per the New York Heart Association (NYHA) 1994 criteria.
25. Patients with a history of, or suspected, demyelinating disease of the central nervous system (e.g., multiple sclerosis or optic neuritis).
26. Patients having had major surgery (including joint surgery) within 8 weeks prior to Screening, or having planned surgery within 6 months after entering the trial.
27. Patients with a current or recent history, as determined by the Investigator, of severe, progressive, and/or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, or neurological disease.
28. Patients with clinically significant laboratory abnormalities (e.g., liver function tests >2x ULN, creatinine >ULN or WBC <3.0x109/L).
29. Patients with any other condition which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the trial.

Trial population

In the trial population, 50% of patients recruited had to meet definition of AS according to the modified NY criteria. Of the remaining 50% of patients, at least 50% had to meet ASAS imaging criteria and the remainder could be enrolled based on clinical criteria only. In order to fulfill the imaging criteria, MRIs had to be read by a radiologist and x-ray and MRI reports had to be included in the source documentation. In addition, no more than 40% of patients were to be secondary failures to anti-TNF-alpha.

Reviewer's comments: Although Protocol Amendment 1 specified that x-rays and MRIs documenting sacroiliitis were to be read by a radiologist, both rheumatologists and radiologists reviewed x-rays and MRIs.

Treatments in trial AS001:
Certolizumab pegol was supplied as a sterile, clear, colorless to slightly yellow liquid solution in 1mL single use glass prefilled syringe (PFS) with a 25G ½-inch thin wall needle for SC injection. Placebo was supplied in a PFS with a 25G ½-inch thin-wall needle. Patients were randomized 1:1:1 to 1 of 3 treatment groups:

- Placebo
- Certolizumab 200mg Q2W after 3 loading doses of 400mg at Weeks 0, 2, and 4
- Certolizumab 200mg Q4W after 3 loading doses of 400mg at Weeks 0, 2, and 4

The product was injected into the lateral abdominal wall and upper outer thigh.

Patients were allocated to treatment in a 1:1:1 ratio (certolizumab 200mg Q2W: certolizumab 400mg Q4W: placebo) and randomization was stratified by site, fulfillment of modified NY criteria according to local interpretation of screening sacroiliac x-rays, and prior anti-TNF-alpha exposure. Placebo subjects who utilized the early escape option were re-randomized at Week 16 in a 1:1 ratio (certolizumab 200mg Q2W: certolizumab 400mg Q4W) stratified by fulfillment of modified NY criteria and prior anti-TNF-alpha exposure. Subjects originally randomized to placebo who completed Week 24 were re-randomized at Week 24 in a 1:1 ratio (certolizumab 200mg Q2W: certolizumab 400mg Q4W) stratified by fulfillment of modified NY criteria and prior anti-TNF-alpha exposure.

Selection of doses in the trial:
No formal dose-ranging studies were conducted with certolizumab for the proposed axial SpA indication. In the single phase 3 trial performed to support approval of certolizumab for axial SpA, the Sponsor evaluated the effect of two different frequencies of administration, Q2W and Q4W as follows:

- Certolizumab 200mg Q2W after 3 loading doses of 400mg at Weeks 0, 2, and 4
- Certolizumab 400mg Q4W after 3 loading doses of 400mg at Weeks 0, 2, and 4

The cumulative doses administered over time were the same for both treatment groups. The doses selected for this trial were based on doses shown to have a favorable risk-benefit profile for the treatment of patients with RA. The three TNF-inhibitors currently approved for AS (adalimumab, etanercept, and golimumab) use the same dosing regimen for AS and RA.

Concomitant medications in Trial AS001:

The following axial SpA medications/treatments were allowed during this trial from Baseline onward, with the specified restrictions:

- NSAIDs/cyclooxygenase-2 inhibitors: doses were to be stable in the 2 weeks prior to an arthritis assessment
- Analgesics (e.g., acetaminophen or paracetamol, narcotics) were permitted except ad hoc as needed (prn) usage within the 24-hour period prior to any assessments
- Corticosteroids:
    - Oral (maximum allowed ≤10mg daily total prednisone equivalent)
        - Subjects were permitted to change their oral corticosteroid therapy dose equivalent and regimen only after Week 48
    - Intra-articular (ia)
        - Only after the first 48 weeks of the trial, 1 ia injection of up to 50mg prednisone equivalent could have been given at most every 4 months.
    - Intravenous (iv)
        - Only after the first 48 weeks of the trial, hydrocortisone administered iv only for the purposes of stress dosing for a surgical procedure under general or spinal anesthesia was permitted.
- Specific sDMARDs only (SSZ and/or HCQ and/or MTX: maximum SSZ ≤3g daily; HCQ ≤400mg daily; MTX ≤25mg weekly allowed. No change in dose or dose regimen was allowed during the first 48 weeks of the trial except for reasons of intolerance, where the sDMARD dose could be decreased but not discontinued. Changes in dosages were permitted after the first 48 weeks of the trial. No change was permitted in the route of administration for MTX (intramuscular [im], sc, or oral) in the first 48 weeks of the trial.

Prohibited Therapies in Trial AS001

Use of the following concomitant medications was prohibited during the trial, except where indicated:

- Corticosteroids (administered im/iv/ia) during the first 48 weeks of the trial. After the first 48 weeks, corticosteroids were permitted only as described in concomitant medications
- Hyaluronic acid administered ia.
- Specific sDMARDs (e.g., azathioprine, cyclosporine, cyclophosphamide, mycophenolic acid, leflunomide).
- Biologics (anti-TNF-alpha medications: infliximab, adalimumab, etanercept, golimumab; ABA; commercially available certolizumab, denosumab; anti-CD20; tocilizumab; alefacept, efalizumab, ustekinumab; also any other biological response modifiers which were not licensed for the treatment of AS or axial SpA).

Patient Stopping Rules in Trial AS001

Patients were free to withdraw from the trial at any time. Patients were to be withdrawn from the trial if any of the following events occurred:

1. Development an illness that would have interfered with his/her continued participation.
2. Noncompliant with the trial procedures or medications in the opinion of the Investigator (e.g., nonadherence to anti-TB therapy).
3. Subject took prohibited concomitant medications as defined in this protocol.
4. Subject withdrew his/her consent.
5. There was confirmation of a pregnancy during the trial, as evidenced by a positive pregnancy test.
6. The Sponsor or a regulatory agency requested withdrawal of the subject.

Trial monitoring and evaluations for trial AS001:
Trial monitoring and evaluations for trial AS001 are presented in Table 11.

Table 11: Overview of monitoring in trial AS001

Protocol Activity	Scr[a]	BL	Weeks																													
	-5 to -1	0	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30 H[b]	32	34 H[b]	36	38 H[b]	40	42 H[b]	44	46 H[b]	48 & 96	Every 4 wks H[b]	Every 4 wks[c]	Every 12 wks[c]	158 or W/D	SFU[d]
Inclusion/ exclusion	X	X																														
Informed consent	X																															
Demographics	X																															
Medical history (including axSpA history)	X																															
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	X	X
Hematology/ biochemistry/ urine/ CRP	X[f]	X[g]	X	X	X		X		X		X	X	X		X	X	X				X						X			X	X	X
Pregnancy test[h]	X	X			X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	
PE[i]	X	X	X	X	X		X		X		X	X	X		X	X	X				X						X			X	X	X
Chest x-ray[j]	X																										X				X	
TB test[k]	X																										X					
TB questionnaire	X	X							X						X						X						X			X	X	
Dispense daily pain diary		X	X	X																												
Collect daily pain diary			X	X	X																											
Sacroiliac joint x-ray[l]		X																														
Spine x-ray and MRI[m]		X							X																		X				X	

Protocol Activity	Scr[a]	BL	Weeks																														
	-5 to -1	0	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30 H[b]	32	34 H[b]	36	38 H[b]	40	42 H[b]	44	46 H[b]	48 & 96	Every 4 wks H[b]	Every 4 wks[c]	Every 12 wks[c]	158 or W/D	SFU[d]
BASMI & Spinal mobility[n]	X	X	X	X	X		X		X		X	X	X		X	X	X		X		X		X		X		X		X	X	X	
BASDAI	X	X	X	X	X		X		X	X	X	X	X		X	X	X				X						X			X	X	
BASFI		X	X	X	X		X		X	X	X	X	X		X	X	X				X						X			X	X	
SF-36		X			X		X		X		X		X		X		X				X						X			X	X	
AsQoL		X	X	X	X		X		X		X	X	X		X	X	X				X						X			X	X	
MOS Sleep Scale		X			X		X		X		X		X		X		X				X						X			X	X	
EQ-5D		X			X		X		X		X		X		X		X				X						X			X	X	
MASES		X	X	X	X		X		X		X	X	X		X	X	X				X						X			X	X	
Total & nocturnal spinal pain		X	X	X	X		X		X	X	X	X	X		X	X	X				X						X			X	X	
Subject's Global assessment		X	X	X	X		X		X	X	X	X	X		X	X	X				X						X			X	X	
Investigator's AS assessment[o]		X	X	X	X		X		X	X	X	X	X		X	X	X				X						X			X	X	
Productivity[p]		X			X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	
Resources utilization[q]		X			X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	
PASS & Physician Acceptable Symptomatic State		X	X	X	X		X		X		X	X	X		X	X	X				X						X			X	X	
PGIC									X						X																	
CZP plasma concentration &		X	X	X	X				X		X				X												X			X[r]	X	X

APPEARS THIS WAY ON ORIGINAL

Protocol Activity	Scr[a]	BL	Weeks																												
	-5 to -1	0	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48 & 96	Every 4 wks[b]	Every 4 wks[c]	Every 12 wks[c]	158 or W/D	SFU[d]
																		H[b]		H[b]		H[b]		H[b]		H[b]						
anti-CZP Abs																																
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	X	X
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	X	X
IVRS	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	X	X
Study drug sc[b]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X[b]	X	X[b]	X	X[b]	X	X[b]	X	X[b]	X	X		

Abs=antibodies; AEs=adverse events; AsQoL=Ankylosing Spondylitis Quality of Life; axSpA=axial spondyloarthritis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; BL=Baseline; CRP=C-reactive protein; CZP=certolizumab pegol; EQ-5D=EuroQoL Health Status Questionnaire; H=home, no site visit; IVRS=Interactive Voice Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MOS=Medical Outcomes Study; MRI=magnetic resonance imaging; PASS=Patient's Acceptable Symptomatic State; PE=physical exam; PGIC=Patient's Global Impression of Change; PPD=purified protein derivative; sc=subcutaneously; Scr=Screening; SF-36=Short-Form 36-item Health Survey; SFU=Safety Follow-Up; TB=tuberculosis; W/D=Withdrawal; wks=weeks.

[a] Select sites could have conducted prescreening activities, and prior to these activities, subjects were to read and sign a separate informed consent form that had been approved by an IEC/IRB and the Sponsor, and which complied with regulatory requirements.

[b] H=home, no site visit. Self administration will be done at home by the subject Q4W starting at Week 30. Demonstration and training on self administration at Weeks 26 and 28.

[c] After Week 48.

[d] SFU: Week 166 or 10 weeks after last dose of study medication.

[e] Pulse rate, systolic and diastolic blood pressures, temperature, and respiration rate are to be measured. Weight to be measured at Screening, Baseline, Weeks 12, 16, 24, 48, 96, and at Completion at Week 158/Withdrawal. Height was measured at the Baseline Visit only.

[f] Testing to rule out hepatitis B surface antigen and antibodies to hepatitis C was done at Screening only.

[g] Testing for HLA-B27 was performed at Baseline only.

[h] Pregnancy testing for women of childbearing potential was serum testing at the Screening Visit and urine testing at other visits.

[i] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Extra-articular assessments to be performed at Baseline, Weeks 4, 12, 16, 20, 24, 28, 36, 48, 72, 96, 120, 144, and at Completion at Week 158/Withdrawal.

[j] Screening chest x ray must have occurred within 3 months prior to Screening Visit and repeated at Weeks 48, 96, and 158 only.

[k] PPD skin test. Elispot (QuantiFERON TB GOLD test if Elispot is not locally available) is permitted only if previously documented severe positive PPD reaction. The TB test will be repeated at Week 48 and Week 96 for subjects with a previously negative TB test result.

[l] Sacroiliac joint x-rays were performed at Baseline for all subjects. A sacroiliac joint x-ray performed ≤12 weeks prior to the Baseline Visit could have been used as the Baseline assessment provided that the film could be submitted and met the requirements for central reading.

[m] At selected sites only, spine x-ray to be performed at Baseline, Week 12, Week 96, and at W/D if subject withdraws prior to Week 96. Magnetic resonance imaging to be performed at Baseline, Week 12, Week 48, Week 96, and at W/D if subject withdraws prior to Week 96.

[n] Occiput to wall distance; chest expansion; and BASMI, which includes modified Schober test, lateral spinal flexion, cervical rotation, tragus to wall distance, and maximal intermalleolar distance.

[o] Includes swollen and tender joint counts and Physician's Global Assessment of Disease Activity.

[p] Includes WPS and socio professional status.

[q] Includes concomitant medical procedures, health care provider consultations not foreseen by the protocol, hospitalizations/emergency room visits.

[r] Only every 24 weeks.

Source: AS001 Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, Table 3-3, pages 47-50

Efficacy Endpoints

Primary Efficacy Endpoint: The primary efficacy endpoint in trial AS001 was the proportion of patients with an **Assessment in Ankylosing Spondylitis (ASAS) 20** response at week 12. A patient was classified as having achieved an ASAS20 response if both of the following were achieved:

1. An improvement of 20% and an absolute improvement of ≥1 unit (on a scale of 0 to 10) from Baseline in ≥ 3 of the following 4 domains:
   - Patient's global assessment (VAS 0 to 100)
   - Pain: assessed by total back pain (VAS 0 to 100)
   - Function: assessed using the Bath AS Functional Index (BASFI) (Table 12)
   - Inflammation: assessed using the last two stiffness assessments in the Bath AS Disease Activity Index (BASDAI) (Table 12)

2. Absence of deterioration from baseline (where deterioration is defined as a net worsening of > 1 unit [on a scale of 0 to 10]) in the potential remaining domain

The ASAS criteria for 40%, 50%, or 70% improvement are defined as relative improvements of at least 40%, 50%, or 70% and absolute improvement of at least 2 units on a 0 to 10 numerical rating scale (NRS) in at least 3 of the 4 domains and no worsening at all in the remaining domain.

Ranked **key secondary efficacy variables** that were analyzed were:

1. **ASAS20** response at week 24
2. Change from baseline in **BASFI** to Weeks 12 and 24 (Table 12)
3. Change from Baseline in **BASDAI** to Weeks 12 and 24 (Table 12)
4. Change from Baseline in **BASMI linear** to Weeks 12 and 24 (Table 12, Table 13)

Table 12: The Bath AS Function Index (BASFI), Bath AS Disease Activity Index (BASDAI), and the Bath AS Metrology Index (BASMI)

Instrument	Definition	Range
Bath AS Functional Index (BASFI)	A functional instrument (a higher score indicates worse function) based on the patient's assessment of his/her ability to perform 10 selected activities during the past week using a visual analogue scale ranging from easy to impossible. The BASFI is the mean of these 10 questions.	0 (easy) to 10 (impossible)
Bath AS Disease Activity Index (BASDAI)	A summary of 6 self-assessments (i.e., fatigue, spinal pain, joint pain, enthesitis, overall level of morning stiffness, and duration of morning stiffness). The first 4 scales are weighted by 0.2 and the last two are weighted by 0.1. The mean of the last two scales provide an assessment of stiffness that is used in the ASAS.	0 (none) to 10 (very severe)
Bath AS Metrology Index (BASMI)	Comprises the sum of 5 measures of hip and spine mobility [i.e. tragus-to-wall, lumbar flexion (modified Schober test), cervical rotation, lateral lumbar flexion, and intermalleolar distance] that are each categorized as 0 (mild), 1 (moderate), or 2 (severe)	0 to 10
BASMI linear	The same as BASMI, except the 5 measures are scored according to the BASMI linear definition (Table 13) and then the mean of the 5 scores is taken.	0 to 10

Table 13: BASMI linear definitions

S=(21.1cm-A)/2.1cm	For the lateral lumbar flexion (mean right/left)
S=(A-8cm)/3cm	For the tragus-to-wall distance (mean right/left)
S=(7.4-A)/0.7cm	For the lumbar flexion (modified Schober)

S=(124.5cm-A)/10cm	For the maximal intermalleolar distance
S=(89.3°-A)/8.5°	For the cervical rotation (mean right/left)
Always with the additional condition 0≤S≤10	

Abbreviations: A=assessment; S=score
Source: AS001 Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, page 57

Other pre-specified secondary efficacy endpoints:

1. Change from Baseline in spine Ankylosing Spondylitis spine MRI score for activity (**ASspiMRI-a)** in the Berlin modification (MRI parameter) to Week 12. The ASspiMRI-a is a scoring system with a concentration on STIR sequences without other fat saturation techniques. The scoring system quantifies changes in 23 vertebral units (VU) of the spine (from C2 to S1). A VU is defined as the region between 2 virtual lines though the middle of each vertebra. Active inflammation is scored by grading the degree of bone marrow edema from 0 to 3 in 1 dimension on 1 or more consecutive slices that represent the highest level of inflammation in a particular VU. Total spine ASspiMRI-a score in the Berlin modification can range from 0 to 69.

2. Change from Baseline in sacroiliac Spondyloarthritis Research Consortium of Canada **(SPARCC) scores** (MRI parameter) to Week 12. The SPARCC scoring method for lesions found on MRI is based on an abnormal increased signal on the short-tau-inversion recovery (STIR) sequence, representing bone marrow edema (defined as an increased signal in bone marrow on a T2-weighted sequence). Total sacroiliac joint SPARCC scores can range from 0 to 72.

3. **ASAS20 response** at Weeks 1, 2, 4, 8, 14, 16, 18, and 20

4. **ASAS40, ASAS50, ASAS70, ASAS5/6 response** at Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20, and 24. The **ASAS5/6 response** is defined as at least 20% improvement in 5 out of the following 6 domains: BASFI, total back pain score (VAS), patient global disease activity score (VAS), inflammation [questions 5 and 6 of the BASDAI regarding morning stiffness], lateral lumbar flexion from BASMI, and CRP.

5. Change from Baseline in all individual **ASAS core components** at Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20, and 24
- Patient's Global Assessment of Disease Activity (PTGADA)
- Total and nocturnal spinal pain NRS (Table 14)
- BASFI (Table 12)
- Average of Questions 5 and 6 of the BASDAI concerning morning stiffness

6. **ASAS partial remission responder** at Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20, and 24. The **ASAS partial remission response** is defined as a score of ≤2 units on a 0 to 10 unit scale in all 4 domains in the ASAS response.

7. Change from Baseline in the **Short-Form 36-item Health Survey (SF-36) Physical Component Summary** (PCS) to Weeks 4, 8, 12, 16, 20, and 24

8. Change from Baseline in the **SF-36 Physical Function domain** to Weeks 4, 8, 12, 16, 20, and 24

9. Change from Baseline in **BASDAI** (Table 12) to Weeks 1, 2, 4, 8, 14, 16, 18, and 20

10. **BASDAI50 responders** at Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20, and 24. **BASDAI50** responder is defined as 50% improvement from Baseline in BASDAI (Table 12).

11. Change from Baseline in **Fatigue** (NRS) (from BASDAI) to Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20, and 24

12. Change from Baseline to Weeks 1, 2, 4, 8, 12, 16, 20, and 24 in:
- **BASMI linear** (not at Weeks 12 and 24) (Table 12)
- Lumbar flexion (modified Schober test)
- Tragus to wall distance
- Occiput to wall distance
- Chest expansion
- Cervical rotation
- Maximal intermalleolar distance
- Lateral side flexion

13. Change from Baseline in **daily pain scores** to Week 4

14. Change from Baseline in c-reactive protein (**CRP)** to Weeks 1, 2, 4, 8, 12, 16, 18, 20, and 24

15. Change from Baseline in Ankylosing Spondylitis Quality of Life (**ASQoL**) to Weeks 1, 2, 4, 8, 12, 16, 18, 20, and 24 (Table 14).

The Sponsor identified pre-specified multiple other endpoints related to assessment of functional status, pain, and overall quality of life at various time points. This document will not review the results of other specific endpoints.

Table 14: Other measures of efficacy in trial AS001

Instrument	Definition
Total and nocturnal pain	Assessed with the questions: "How much pain of your spine due to spondyloarthritis do you have?" and "How much pain of your spine due to spondyloarthritis do you have at night"
ASQoL	18-item questionnaire validated in AS to assess health related quality of life

Statistics in Trial AS001:

A

Populations: The populations specified in the statistical analysis plan dated March 22, 2012 were:

- **Enrolled set**: all patients who gave informed consent
- **Randomized set**: all patients randomized into the trial with an intention to treat
- **Safety set**: all patients in the randomized set who received at least one dose of trial medication
- **Full analysis set**: all patients in the randomized set who received at least 1 dose of trial medication, had a valid baseline, and a valid post-baseline efficacy measurement for the ASAS20 (data on ASAS measurement through to Week 12)
- **Per-protocol set**: patients in the full analysis set who had completed a minimal exposure of 12 weeks in the treatment regimen without any major protocol deviations that could have influenced the validity of the data for the primary efficacy variables.
- **Completer sets**: patients in the full analysis set who completed 24 weeks of the randomized treatment regimen with valid 24 week measurements
- **Pharmacokinetic per-protocol set**: patients from the safety set who had valid PK assessments according to the Applicant's SOPs.
- **Magnetic resonance imaging set**: patients participating in the MRI sub-study who had valid MRI assessments at baseline and Week 12

Database locks: The 2 database locks occurred at Weeks 24 and 48.

Methods for the Primary Efficacy Endpoint: The primary efficacy endpoint was the proportion of ASAS20 responders at Week 12. The response proportions for certolizumab and placebo were compared using a 2-sided Wald asymptotic test with α=0.05.

Handling of Missing Data for the Primary Efficacy Endpoint: If patients had missing data but had data for at least 1 ASAS component at Week 12, the following rules were applied:

- For any ASAS component, if all the component values were missing from Baseline through Week 12, the percent improvement from Baseline at Week 12 for that component was imputed with 0%
- For any ASAS component, if the component value at Week 12 was missing and the Baseline value was present, the missing component was replaced by the last non-missing observation (LOCF).
- For any ASAS component, if the component value at Baseline was missing but a post-Baseline value was observed prior to or at Week 12, the median component value of all subjects with non-missing Baseline values in the same stratum, ie, modified NY Criteria for AS (yes/no) based on the CRF assessment at Screening, were used to impute the Baseline value.

If the Baseline value of an ASAS component was 0, then for the purposes of calculating ASAS20, the percent change from Baseline was determined as follows (zero divisor rule):

- If the post-Baseline component value was also 0, the percent change was set to equal 0;
- If the post-Baseline component value was >0, then the percent change was calculated as though the Baseline value were 0.1.
- If all ASAS20 components at Baseline were missing, no Screening observation was used and the subject was regarded as nonresponder throughout the trial.

If all ASAS20 components at Baseline were missing, no Screening observation was used and the subject was regarded as nonresponder throughout the trial.

Methods for the Secondary Efficacy Endpoints: The secondary efficacy endpoints were ranked. The first endpoint was to be tested at α=0.05; if the null hypothesis was rejected, the next hypothesis in the sequence was to be tested at α=0.05; this process continued until the null hypothesis for a particular variable was accepted. The predefined order of hypotheses testing, each at a 2-sided 5% alpha level versus placebo, was performed in the following sequence for the dose regimens and endpoints:

1. ASAS20 response at Week 12 for certolizumab 200mg Q2W
2. ASAS20 response at Week 12 for certolizumab 400mg Q4W
3. ASAS20 response at Week 24 for certolizumab 200mg Q2W
4. ASAS20 response at Week 24 for certolizumab 400mg Q4W
5. Change from Baseline in BASFI at Week 12 for CZP certolizumab Q2W and certolizumab 400mg Q4W combined
6. Change from Baseline in BASDAI at Week 12 for certolizumab 200mg Q2W and certolizumab 400mg Q4W combined
7. Change from Baseline in BASFI at Week 24 for certolizumab 200mg Q2W and certolizumab 400mg Q4W combined
8. Change from Baseline in BASDAI at Week 24 for certolizumab 200mg Q2W and certolizumab 400mg Q4W combined
9. Change from Baseline in BASMI at Week 12 for certolizumab 200mg Q2W and certolizumab 400mg Q4W combined
10. Change from Baseline in BASMI at Week 24 for certolizumab 200mg Q2W and certolizumab 400mg Q4W combined

All are versus placebo. The primary analysis of the variables subject to the hierarchical test procedure was performed for the RS by imputation of missing values. The ASAS20 response at Weeks 24 were analyzed utilizing the same approach as for Week 12. In addition, placebo patients who escaped early were considered no responders from the time the escape medication was initiated. The changes from Baseline in the BASDAI, BASFI, and BASMI at Weeks 12 and 24 were compared between

In general and if not specifically stated otherwise, for all efficacy assessments LOCF was applied for all analyses based up analyses sets with imputations.

The hierarchical testing procedure was carried out on the overall axial SpA population and not on the AS and nr-axSpA subgroups. It is important to note that the efficacy analyses were primarily conducted on the entire axial SpA population (referred to as the overall axial SpA population) and thus are the primary focus of the results discussions. Of note, the Sponsor performed multiple analyses in the subgroups of patients defined as AS and nr-axSpA. This will be further discussed in Section 6.1.3 (Subject disposition) and 6.1.2 (Analyses of Secondary Endpoints).

Definitions of Safety Endpoints in Trial AS001:

AE Definition

An AE was defined as any untoward medical occurrence in a patient which did not necessarily have a causal relationship with the treatment. An AE could therefore have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medical product, whether or not related to the investigational medical product. Laboratory values were to be considered AEs if they were out of the reference range and of clinical relevance or changed from a subject's baseline and of clinical relevance. Pre-existing physical findings (including vital sign measurements) that worsened compared with Baseline and were clinically relevant, were considered AEs.

SAE Definition

An AE that met 1 or more of the following criteria was considered an SAE:

- Death
- Life-threatening
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect
- An important medical event that, based upon appropriate medical judgment, may have jeopardized the patient and may have required medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious
- Initial inpatient hospitalization or prolongation of hospitalization. A subject admitted to a hospital, even if released on the same day, met the criteria for the initial inpatient hospitalization. An ER visit that resulted in admission to the hospital would have also qualified for the initial inpatient hospitalization criteria. However, ER visits that did not result in admission to the hospital would not have qualified for these criteria and, instead, were to be evaluated for one of the other criteria in the definition of serious (e.g., life-threatening or important medical event).

Coding dictionaries

The Medical Dictionary for Regulatory Activities (MedDRA®) version 14.1 was utilized for coding of AEs and conditions in the medical history. The World Health Organization Drug Dictionary (WHO Drug) version June 2011 was applied for medications. Medical procedures were not coded. The Rheumatology Common Toxicity Criteria (RCTC Version 2) was utilized for identification of marked abnormal laboratory values.

6 Review of Efficacy

Efficacy Summary for Axial Spondyloarthritis

Trial AS001 was submitted as the primary source of efficacy data for certolizumab in the treatment of axial SpA. The trial consisted of a 24-week double-blind period followed by a 110-week open label extension. The Sponsor submitted data to Week 24. The primary efficacy analysis was at Week 12. The primary endpoint was the proportion of patients with an ASessment in Ankylosing Spondylitis (ASAS) 20 response. Secondary efficacy analyses were performed at Weeks 12 and 24. This trial was well-controlled and had endpoints that are considered acceptable for efficacy evaluations in AS.

In the pre-specified primary analyses, certolizumab met the primary and key secondary endpoints. Baseline data suggest important genetic and demographic differences between the AS and nr-axSpA subgroups within the broader axial SpA population. Further, functional impairment, disease activity, and objective markers of inflammation appeared to differ for these subgroups. Given the heterogeneity of axial SpA, it was unclear if the magnitude of the treatment effect was similar in these subgroups. In trial AS001, patients were classified into the subgroups AS and nr-axSpA based on the presence or absence of radiographic changes consistent with AS on sacroiliac x-rays at screening. There appeared to be limitations in defining these subgroups based on x-rays given differences in interpretation of sacroiliac x-rays depending on whether the x-rays were evaluated locally or centrally. The differences in classification were especially notable for patients with nr-axSpA.

In order to evaluate if the effect of treatment varied substantially across important subgroups, the Sponsor stratified by these subgroups and evaluated for consistency across the subgroups. Subgroup classification was either by central or local x-ray interpretation. In general, the trends seen in the subgroups were consistent with those demonstrated in the overall population. The magnitude of effect in the subgroups did vary for some endpoints when the subgroup assignment was determined by local or central x-ray assessments. It is important to recognize that certolizumab is not currently approved for the treatment of AS.

We recognize that these subgroup analyses are exploratory and should be interpreted cautiously. In general, the best test of validity in subgroup analyses is not significance, but independent substantiation of results. Further, based on central x-ray classification, the majority of patients had AS, and it was unclear if the results could be extrapolated to the broad population of active axial SpA.

6.1 Indication

UCB proposed the following indication in the original application: "treatment of adult patients with active axial spondyloarthritis, including patients with ankylosing spondylitis." Following the Advisory Committee Meeting on July 23, 2013, the Sponsor proposed the following indication in a submission dated August 9, 2013: "treatment of

(b) (4)

6.1.1 Methods

Trial AS001 served as the critical trial for the evaluation of the efficacy of certolizumab in the treatment of axial spondyloarthritis. This trial was well-controlled and utilized endpoints used in other programs to support approval for AS. Previous TNF-inhibitors have utilized one trial to support their efficacy in AS, but for all four of these products, efficacy and safety demonstration in AS followed efficacy and safety demonstration in RA.

Reviewer's comments: It is unclear whether the submitted data from one study, without replication from a second study, are adequate to support efficacy in the broader indication axial SpA.

The sponsor presented efficacy results in the overall axial SpA population and in the subgroups of patients with nr-axSpA and AS. Subgroup classification was based on local interpretation of screening sacroiliac x-rays. The sponsor noted that there was potential misclassification into these subgroups when sacroiliac x-rays were re-done at baseline and read centrally (Section 6.1.3—Subject Disposition). As there are data to suggest that there are potentially important differences between these subgroups and it is unclear if potential misclassification would impact the risk/benefit assessment, additional subgroup analyses were performed based on central x-ray classification.

6.1.2 Demographics

Demographics: Table 15 displays the baseline demographics in trial AS001. In the overall axial SpA population, the three treatment groups had similar baseline demographics. The demographics of the overall axial SpA patients were typical of an AS population—predominantly young males. Most of the patients were white. It is unclear if the baseline demographics in axial SpA are typical of all patients with axial SpA given then minimal epidemiological information available on these patients.

Notably, there were demographic differences in the AS and nr-axSpA subgroups. Specifically, the median age and percentage of male participants were lower in the nr-axSpA subgroup compared with the AS subgroup. The AS and nr-axSpA appear to

represent distinct subgroups with different demographic characteristics.

Of note, the AS and nr-axSpA subgroup classification was based on local sacroiliac x-ray classification. When the AS and nr-axSpA subgroup classification was based on central x-ray classification, similar trends were noted, except the differences in age profiles of patients with AS and nr-axSpA were smaller based on central than local x-ray classification.

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Table 15: Baseline demographics in trial AS001

Characteristic	PBO	CZP 200mg Q2W	CZP 400mg Q4W
Overall axial SpA population, N	107	111	107
Age (years)			
Mean (SD)	39.9 (12.4)	39.1 (11.9)	39.8 (11.3)
Median (range)	38.0 (19, 68)	36.0 (20, 78)	40.0 (19. 67)
Gender, n (%)			
Male	65 (60.7)	67 (60.4)	68 (63.6)
Female	42 (39.3)	44 (39.6)	39 (36.4)
Race, n (%)			
White	95 (88.8)	102 (91.9)	96 (89.7)
Black	1 (0.9)	1 (0.9)	3 (2.8)
Asian	0	0	1 (0.9))
Weight, mean (kg)	82.1 (18.2)	79.3 (18.6)	83.9 (18.9)
Height, mean (cm)	170.7 (9.7)	171.8 (10.2)	172.8 (9.6)
Combined sites, n (%)			
North America	30 (28.0)	30 (27.0)	28 (26.2)
Latin America	12 (11.2)	9 (8.1)	12 (11.2)
West Europe	21 (19.6)	23 (20.7)	19 (17.8)
East Europe	44 (41.1)	49 (44.1)	48 (44.9)
AS Subgroup, N	57	65	56
Age (years)			
Mean (SD)	41.6 (12.8)	41.0 (10.8)	41.9 (11.5)
Median (range)	41.0 (21, 68)	39.0 (24, 64)	41.5 (19, 66)
Gender, n (%)			
Male	41 (71.9)	47 (72.3)	41 (73.2)
Female	16 (28.1)	18 (27.7)	15 (26.8)
Race, n (%)			
White	51 (89.5)	59 (90.8)	49 (87.5)
Black	0	1 (1.5)	3 (5.4)
Asian	0	0	0
Weight, mean (kg)	82.2 (18.9)	80.5 (17.9)	82.7 (20.3)
Height, mean (cm)	170.0 (9.3)	172.2 (11.2)	172.4 (9.7)
Nr-axSpA subgroup, N	50	46	51
Age (years)			
Mean (SD)	38.0 (11.8)	36.6 (13.0)	37.5 (10.8)
Median (range)	37.0 (19, 68)	33.0 (20, 78)	37.0 (20, 67)
Gender, n (%)			
Male	24 (48.0)	20 (43.5)	27 (52.9)
Female	26 (52.0)	26 (56.5)	24 (47.1)
Race, n (%)			
White	44 (88.0)	43 (93.5)	47 (92.2)
Black	1 (2.0)	0	0
Asian	0	0	1 (2.0)
Weight, mean (kg)	82.1 (17.4)	77.6 (19.6)	85.2 (17.2)
Height, mean (cm)	171.6 (10.1)	171.2 (8.5)	173.2 (9.6)

PBO=placebo; CZP=certolizumab; Q2W=every 2 weeks; Q4W=every 4 weeks; AS=ankylosing spondylitis; nr-axSpA=nonradiographic axial spondyloarthritis; SD=standard deviation; kg=kilogram; cm=centimeter
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 7-1 (109-10), 7-2 (111-2), and 7-3 (113-114)

ASAS classification criteria

Table 16 displays the proportion of patients fulfilling the ASAS classification criteria in the overall trial population. As part of the trial entry criteria, patients were required to fulfill the ASAS classification criteria for axial SpA. There were 7 patients who did not fulfill the ASAS classification criteria, and were therefore protocol violations

The most frequently met criteria were back pain at least 3 months and age of onset less than 45 years (98.8%), sacroiliitis on imaging (79.4%), HLA-B27 positive (71.4%), inflammatory back pain (98.5%), and elevated CRP (88.3%). While MRIs were available for only a subset of patients, it was clear that the majority of the patients had sacroiliitis either on MRI or x-rays.

Table 16: ASAS criteria in trial AS001

Characteristic, n (%)	PBO	CZP 200mg Q2W	CZP 400mg Q4W
Overall axial SpA population, N	107	111	107
ASAS classification criteria fulfilled	104 (97.2)	109 (98.2)	105 (98.1)
Back pain ≥3 months and onset age<45 years	106 (99.1)	109 (98.2)	106 (99.1)
Sacroiliitis on imaging			
Yes	84 (78.5)	90 (81.1)	84 (78.5)
By MRI	31 (29.0)	32 (28.8)	35 (32.7)
By x-ray	57 (53.3)	65 (58.6)	56 (52.3)
Positive HLA-B27	76 (71.0)	81 (73.0)	75 (70.1)
Inflammatory back pain	105 (98.1)	109 (98.2)	106 (99.1)
Arthritis	61 (57.0)	62 (55.9)	53 (49.5)
Enthesitis	45 (42.1)	35 (31.5)	37 (34.6)
Uveitis	31 (29.0)	23 (20.7)	15 (14.0)
Dactylitis	15 (14.0)	7 (6.3)	11 (10.3)
Psoriasis	7 (6.5)	6 (5.4)	7 (6.5)
Crohn's disease/ulcerative colitis	8 (7.5)	5 (4.5)	5 (4.7)
Elevated CRP	94 (87.9)	99 (89.2)	94 (87.9)
Good response to NSAIDs	38 (35.5)	33 (29.7)	37 (34.6)
Family history of axial SpA	15 (14.0)	14 (12.6)	12 (12.1)

A criteria is considered positive if there was current and/or historical presence of specific factors
ASAS=Assessment in Spondyloarthritis International Society, CRP=c-reactive protein, CZP=certolizumab; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; HLA-B27=human leukocyte antigen B27; MRI=magnetic resonance imaging; NSAIDs=nonsteroidal anti-inflammatory drugs; SpA=spondyloarthritis
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 7-4, pages 120-1

Baseline Disease Characteristics: Table 17 displays the baseline disease characteristics in trial AS001.

No clinically relevant differences in Baseline ASAS criteria were seen between treatment groups. Most of the patients (97.8%) reported inflammatory back pain at Baseline, 80.3% had elevated CRP levels, and 41.5% reported current arthritis at Screening.

In the overall axial SpA population, definitive sacroiliitis determined by x-ray was reported in 54.8% of patients and sacroiliitis by MRI was known in 30.2% of patients.

Patients without evidence of sacroiliitis on MRI could have had a negative MRI or not had an MRI available. Consistent with trial entry criteria, all (100%) of the patients in the AS subpopulation had evidence of sacroiliitis determined by x-ray at screening. A total of 54.4% of subjects in the nr-axSpA subgroup had sacroiliitis detected via MRI.

In general, baseline disease characteristics were similar in the different treatment groups. At baseline, median CRP levels were higher in the placebo group compared to the active trial drug groups. This imbalance may suggest more active disease in the placebo group and might make it more difficult to demonstrate product efficacy.

Patients in the AS subgroup had longer mean duration of back pain (11.9 years versus 8.6 years), higher mean CRP levels (21.3 versus 16.0 mg/L), and higher mean BASMI (4.4 versus 3.1) and BASFI scores (5.7 versus 4.9) than patients in the nr-axSpA subgroup. The mean BASDAI scores were similar between the two subgroups. These findings suggest less functional and mobility limitations in patients with nr-axSpA compared with AS. These differences might be due to a shorter time since diagnosis of disease and less chronic structural damage. In addition, this suggests less systemic inflammation in patients with nr-axSpA compared with patients with AS. There are also genetic differences between the subgroups as the proportion of patients with positive HLA-B27 was higher in patients with AS than nr-axSpA.

Sacroiliac joint and spinal MRIs were performed on patients in the MRI sub-study (n=153) and scored by the SPARCC (sacroiliac joint) and ASspiMRI (spine) scoring methods. The mean baseline SPARCC score was 12.84 in the overall axSpA population, 12.47 in the AS subgroup, and 13.44 in the nr-axSpA subgroup. In the overall population, the majority of patients (68%) had baseline SPARCC scores ≥2. The mean baseline ASspiMRI score was 5.01 in the overall axSpA population, 5.82 in the AS subgroup, and 3.70 in the nr-axSpA subgroup. Thus, patients in the nr-axSpA subgroup had lower spinal inflammation on MRI than patients in the AS subgroup.

Table 17: Baseline disease characteristics in trial AS001

Characteristic	PBO	CZP 200mg Q2W	CZP 400mg Q4W
Overall axial SpA population, N	107	111	107
ASAS classification criteria not fulfilled	3 (2.8)	2 (1.8)	2 (1.9)
Time since diagnosis (years)			
Mean (SD)	7.2 (7.5)	6.3 (7.5)	6.7 (7.4)
Median (range)	4.9 (0-37.9)	3.0 (0.1-32.2)	3.7 (0.1-30.3)
Symptom (back pain) duration (years)			
Mean (SD)	11.3 (10.6)	9.7 (8.9)	10.3 (8.9)
Median	7.7 (0.3-50.9)	6.9 (0.3-34.2)	7.9 (0.3-44.8)
CRP (mg/L), mean (SD)	22.4 (25.9)	17.6 (22.4)	16.9 (21.2)
Testing for HLA-B27, n (%)			
Negative	20 (18.7)	18 (16.2)	21 (19.6)
Positive	87 (81.3)	87 (78.4)	81 (75.7)
Baseline BASDAI scores, FAS, mean (SD)	6.4 (1.7)	6.5 (1.6)	6.4 (1.5)
Baseline BASMI scores, FAS, mean (SD)	4.0 (1.8)	3.7 (1.6)	3.8 (1.7)
Baseline BASFI scores, FAS, mean (SD)	5.5 (2.1)	5.3 (2.3)	5.4 (2.3)
AS Subgroup, N	57	65	56
Time since diagnosis (years)			
Mean (SD)	9.9 (8.5)	7.4 (7.8)	7.5 (7.8)
Median (range)	6.9 (0.5, 37.9)	4.7 (0.2, 31.5)	4.0 (0.3, 29.3)
Symptom (back pain) duration (years)			
Mean (SD)	13.1 (10.8)	10.5 (8.8)	12.4 (10.1)
Median (range)	10.2 (0.3, 50.9)	8.8 (0.3, 32.7)	8.8 (0.3, 44.8)
CRP (mg/L), mean (SD))	25.2 (26.7)	20.5 (27.2)	18.3 (23.0)
Testing for HLA-B27, n (%)			
Negative	9 (15.8)	9 (13.8)	10 (17.9)
Positive	48 (84.2)	53 (81.5)	44 (78.6)
Baseline BASDAI scores, FAS, mean (SD)	6.4 (1.9)	6.5 (1.7)	6.2 (1.3)
Baseline BASMI scores, FAS, mean (SD)	4.7 (1.6)	4.2 (1.6)	4.3 (1.8)
Baseline BASFI scores, FAS, mean (SD)	6.0 (2.0)	5.6 (2.3)	5.7 (2.3)
Nr-axSpA Subgroup, N	50	46	51
Time since diagnosis (years)			
Mean (SD)	4.2 (4.7)	4.6 (6.7)	5.9 (6.8)
Median (range)	3.1 (0, 20.3)	1.8 (0.2, 32.2)	3.4 (0.1, 30.3)
Symptom (back pain) duration (years)			
Mean (SD)	9.2 (10.0)	8.5 (9.1)	8.1 (6.8)
Median (range)	4.5 (0.5, 41.5)	4.8 (0.3, 34.2)	7.3 (0.3, 25.3)
CRP (mg/L), mean (SD)	19.1 (24.9)	13.4 (11.8)	15.5 (19.2)
Testing for HLA-B27, n (%)			
Negative	11 (22.0)	9 (19.6)	11 (21.6)
Positive	39 (78.0)	34 (73.9)	37 (72.5)
Baseline BASDAI scores, FAS, mean (SD)	6.4 (1.5)	6.5 (1.4)	6.6 (1.6)
Baseline BASMI scores, FAS, mean (SD)	3.1 (1.6)	3.1 (1.4)	3.3 (1.5)
Baseline BASFI scores, FAS, mean (SD)	4.9 (2.2)	4.8 (2.2)	5.1 (2.4)

Axial SpA=axial spondyloarthritis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Functional Index; CRP=C-reactive protein; CZP=certolizumab; HLA-B27= human leukocyte antigen B27; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation; AS=ankylosing spondylitis; nr-axSpA=non-radiographic axial spondyloarthritis

Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 7-6, (pages 124-5), 7-7 (126-7), and 7-8 (128-9)

Past medications

The sponsor defined past medications as those taken before the date of first trial medication administration and stopped before the first drug administration in trial AS001. Table 18 displays the proportion of patients who received TNF-inhibitors, disease modifying anti-rheumatic drugs (DMARDs), or nonsteroidal anti-inflammatory drugs (NSAIDs) prior to trial medication administration.

Approximately half of the patients (49%) reported past use of any DMARDs (including TNF-inhibitors). A higher percentage of patients in the placebo group used anti-TNF medications prior to Baseline relative to the active treatment groups (23% versus 14% and 11%, respectively). The two most commonly used DMARDs were sulfasalazine (31%) and methotrexate (17%).

Most (85%) patients reported past use of NSAIDs at Baseline. The treatment groups were well-balanced in the number of patients reporting prior use of any NSAID.

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Table 18: Proportion of patients who received TNF-inhibitors, NSAIDs, or DMARDs prior to trial AS001

	PBO n (%)	CZP 200mg Q2W n (%)	CZP 400mg Q4W n (%)
Overall axial SpA population, N			
Any past DMARD	61 (57)	50 (45)	49 (46)
Methotrexate	24 (22)	16 (14)	14 (13)
Azathioprine	0	1 (1)	2 (2)
Leflunomide	2 (2)	0	2 (2)
Sulfasalazine	36 (34)	31 (28)	32 (30)
Past anti-TNF-alpha	25 (23)	15 (14)	11 (10)
Any past NSAID use	95 (89)	91 (82)	91 (85)
AS Subgroup, N	57	65	56
Any past DMARD	40 (70)	35 (54)	29 (52)
Methotrexate	15 (26)	10 (15)	7 (13)
Azathioprine	0	0	2 (4)
Leflunomide	0	0	1 (2)
Sulfasalazine	27 (47)	22 (34)	19 (34)
Past anti-TNF-alpha	16 (28)	11 (17)	9 (16)
Any past NSAID use	55 (97)	52 (80)	44 (79)
Nr-axSpA Subgroup	50	46	51
Any past DMARD	21 (42)	15 (33)	20 (39)
Methotrexate	9 (18)	6 (13)	7 (14)
Azathioprine	0	1 (2)	0
Leflunomide	2 (4)	0	1 (2)
Sulfasalazine	9 (18)	9 (20)	13 (26)
Past anti-TNF-alpha	9 (18)	4 (9)	2 (4)
Any past NSAID use	40 (80)	39 (85)	47 (92)

PBO=placebo; CZP=certolizumab; Q2W=every 2 weeks; Q4W=every 4 weeks; TNF=tumor necrosis factor; NSAID=nonsteroidal anti-inflammatory drug; DMARD=disease modifying anti-rheumatic drug; AS=ankylosing spondylitis; nr-axSpA=nonradiographic axial spondyloarthritis
Source: Adapted from Efficacy Information Amendment (Module 1.11.3), submitted 6/17/13, table 3, pages 4-6

Concomitant medications

The Sponsor defined concomitant medications as follows:

- All medications started before and still ongoing at the date of first trial drug administration
- All medications that were started during the trial until week 24
- All medications that were started within 70 days after the last double-blind trial drug administration for patients who terminated early

Table 19 displays the use of NSAIDs, DMARDs, or TNF-inhibitors during trial AS001. Use of any concomitant NSAID was reported by 87.7% of patients in the overall axial SpA population. The percentage of patients using concomitant NSAIDs in the AS subgroup was similar to the overall axial SpA population.

Specific concomitant DMARDs were permitted in the trial protocol as detailed in Section 5.3.1 (Trial AS001).

Use of any concomitant DMARDs was reported by 32% of patients overall. The most commonly used DMARDs were sulfasalazine (17%) and methotrexate (15%). The percentage of patients using concomitant DMARDs in the AS subgroup was similar to the overall axial SpA population. The percentage of patients using concomitant DMARDs in the nr-axSpA subgroup was slightly lower than the overall axial SpA population.

The five patients who received other TNF-inhibitors during trial AS001 were terminated early. These patients started another TNF-inhibitor within 70 days after early termination. No patients received another TNF-inhibitor while taking certolizumab.

Table 19: Proportion of patients who received TNF-inhibitors, NSAIDs, or analgesics during trial AS001 (RS)

Characteristic	PBO	CZP 200mg Q2W	CZP 400mg Q4W
Overall axial SpA population, N	107	111	107
Any concomitant NSAID use	92 (86)	97 (87)	95 (89)
Any concomitant DMARD	40 (37)	31 (28)	34 (32)
Methotrexate	18 (17)	14 (13)	18 (17)
Sulfasalazine	20 (19)	17 (15)	19 (18)
TNF-inhibitor	2 (2)	0	3 (3)
Opioids	29 (27)	22 (20)	15 (14)
AS Subgroup, N	57	65	56
Any concomitant NSAID use	51 (90)	59 (91)	51 (91)
Any concomitant DMARD	23 (40)	21 (32)	20 (36)
Methotrexate	9 (16)	8 (12)	11 (20)
Sulfasalazine	12 (12)	13 (20)	14 (25)
TNF-inhibitor	1 (2)	0	1 (2)
Opioids	17 (30)	13 (20)	6 (11)
Nr-axSpA Subgroup, N	50	46	51
Any concomitant NSAID use	41 (82)	38 (83)	44 (86)
Any concomitant DMARD	17 (34)	10 (22)	14 (28)
Methotrexate	9 (18)	6 (13)	7 (14)
Sulfasalazine	8 (16)	4 (9)	5 (10)
TNF-inhibitor	1 (2)	0	2 (4)
Opioids	12 (24)	9 (20)	9 (18)

PBO=placebo; CZP=certolizumab; Q2W=every 2 weeks; Q4W=every 4 weeks; TNF=tumor necrosis factor; NSAID=nonsteroidal anti-inflammatory drug; DMARD=disease modifying anti-rheumatic drug; AS=ankylosing spondylitis; nr-axSpA=nonradiographic axial spondyloarthritis
Source: Adapted from Efficacy Information Amendment (Module 1.11.3), submitted 6/17/13, table 4, pages 6-7

6.1.3 Subject Disposition

Disposition: Table 20 displays the patient disposition through Week 24 in trial AS001. A total of 325 patients with axial SpA according to the ASAS classification criteria were randomized in AS001. At Week 0, a total of 218 patients were randomized to certolizumab and 107 were randomized to placebo. At Week 16, fifty-six (56) placebo-

escape patients were re-randomized to certolizumab 200mg Q2W (27 patients) or certolizumab 400mg Q4W (29 patients). Most (91.7%) patients completed the double-blind treatment period of 24 weeks. A slightly higher proportion of patients discontinued in the placebo group than the certolizumab groups.

Table 20: Patient disposition through 24 weeks in trial AS001

	Overall population			AS population		
	Placebo	CZP 200 Q2W	CZP 400 Q4W	Placebo	CZP 200 Q2W	CZP 400 Q4W
Randomized, n	107	111	107	57	65	56
Escaped, n	56 (27 CZP 200 Q2W)	---	---	30 (16 CZP 200 Q2W)	---	---
Completed 24 weeks, n	95 (54 escaped patients)	105	98	52 (29 escaped patients)	60	52
Discontinued, n (%)	12 (11.2)	6 (5.4)	9 (8.4)	5 (8.8)	5 (7.7)	4 (7.1)

CZP=certolizumab; ITT=intention to treat; Q2W=every 2 weeks; Q4W=every 4 weeks
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, figures 7-1 (page 106) and 7-2 (107)

Comparison of local investigator's and central reader's assessment of x-rays

The Sponsor identified differences in the local interpretation of screening sacroiliac x-rays and central interpretation of baseline sacroiliac x-rays. Patients who met the ASAS classification criteria were enrolled into the AS001 trial. Principal investigators determined whether patients met the criteria based upon their medical history including any routine imaging data. At screening, the most current x-ray before screening was used for determination of sacroiliitis and was read locally. These x-rays could be evaluated by either rheumatologists or radiologists, but were not evaluated by a central reader. Based on the local investigator's assessment, patients were classified as either AS or nr-axSpA. At baseline, sacroiliac x-rays were performed. These x-rays were assessed via a central reading system utilizing two readers, with adjudication by a third reader when the two readers did not agree. The central readers were blinded to both the assigned subgroup and the treatment group. A comparison of the investigator's assessment of x-rays at screening and the central reader's assessment at baseline is shown in Table 21. A high proportion of patients were reclassified when x-rays were evaluated centrally rather than locally. A total of 21% of patients classified as having AS by local investigators were felt not to have definitive sacroiliitis when x-rays were evaluated centrally. A total of 51% of patients were assessed by local investigators as not having AS based on screening x-rays were considered by the central readers to have sacroiliitis on baseline x-rays. These results highlight the higher inter-reader variability in diagnosis of sacroiliitis on x-ray. It is possible that some of the differences were secondary to progression of radiographic changes over time, however given the overall discordance in interpretations, this seems less likely. Based on baseline central reader's assessment, 184 patients had AS and 98 patients had nr-axSpA in trial AS001. Thus, a limited number of patients had nr-axSpA and a small subset of these patients

did not have sacroiliitis on MRI. It is unclear if this patient population is adequate to support the broad indication active axial SpA.

Table 21: Comparison of investigator's and central reader's assessment of sacroiliac x-rays

Investigator's assessment (screening)	Central reader's assessment (baseline)†		
	mNY-Yes n (%)	mNY-No n (%)	Total N
mNY-Yes (N=178)	112 (79)	29 (21)	141
mNY-No (N=147)	72 (51)	69 (49)	141

† Central reads were not performed for 43 patients as x-rays were not available. Of the 43 patients, 37 had been classified as AS by the Investigator and 6 had been classified as non-radiographic axial SpA by the Investigator
mNY=modified New York Criterion
Yes=fulfilling modified New York Criterion for ankylosing spondylitis
No=not fulfilling the modified New York Criterion for ankylosing spondylitis
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 7-11, page 135

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoints in trial AS001 was the proportion of patients with an ASsessment in Ankylosing Spondylitis (ASAS)20 response at Week 12 for each certolizumab dose compared to placebo. A key secondary endpoint was the proportion of patients with an ASAS20 response at Week 24 for each certolizumab dose compared to placebo. A patient was classified as having achieved as an ASAS20 response at Week 12 if both of the following were achieved:

1. An improvement of 20% and an absolute improvement of ≥1 unit (on a scale of 0 to 10) from Baseline in ≥ 3 of the following 4 domains:
    - Patient's global assessment (VAS 0 to 10)
    - Pain: assessed by total back pain (VAS 0 to 10)
    - Function: assessed using the Bath AS Functional Index (BASFI)
    - Inflammation: assessed using the last two stiffness assessments in the Bath AS Disease Activity Index (BASDAI)
2. Absence of deterioration from baseline (where deterioration is defined as a net worsening of > 1 unit [on a scale of 0 to 10]) in the potential remaining domain

See Table 22 for definitions of BASFI and BASDAI.

Table 22: The Bath AS Function Index (BASFI) and Bath AS Disease Activity Index (BASDAI)

Instrument	Definition	Range
Bath AS Functional Index (BASFI)	A functional instrument (a higher score indicates worse function) based on the patient's assessment of his/her ability to perform 10 selected activities during the past week using a visual analogue scale ranging from easy to impossible. The BASFI is the mean of these 10 questions.	0 to 10
Bath AS Disease Activity Index (BASDAI)	A summary of 6 self-assessments (i.e., fatigue, spinal pain, joint pain, enthesitis, overall level of morning stiffness, and duration of morning stiffness). The first 4 scales are weighted by 0.2 and the last two are weighted by 0.1. The mean of the last two scales provide an assessment of stiffness that is used in the ASAS.	0 (none) to 10 (very severe)

Source: FDA generated

Table 23 displays the proportion of ASAS20 responders at Week 12 in trial AS001 in the overall axial SpA population, which was the pre-specified analysis. Both certolizumab treatment groups had a greater proportion of ASAS20 responders at Week 12 compared to the placebo group. These results were statistically significant and the absolute treatment effect sizes between the certolizumab groups and the placebo groups were 19% and 25% for the 200mg Q2W and 400mg Q4W groups, respectively. The magnitude of effect was slightly higher for the 400mg Q4W dose than the 200mg Q2W dose. ASAS20 response at Week 24 was a key secondary endpoint, but is presented here for ease of reference. The efficacy results were maintained at 24 weeks.

Table 23: ASAS20 responses at Week 12 and Week 24 in overall axial SpA population (RS)

	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W + CZP 400mg Q4W
Overall axial SpA population, N	107	111	107	218
Week 12				
Responders (%)	38	58	64	61
Difference to PBO (%)	---	19	25	22
P-value	---	0.004	<0.001	<0.001
Week 24				
Responders (%)	29	67	70	68
Difference to PBO (%)	---	38	41	39
P-value	---	<0.001	<0.001	<0.001

ASAS20=ASsessment in Axial Spondyloarthritis International Society 20% response criteria; axial SpA=axial spondyloarthritis; CZP=certolizumab; –=not applicable; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, tables 8-2 (page 140), 8-3 (142)

While not specified as primary analyses, the Sponsor also evaluated ASAS20 response at Weeks 12 and 24 in the subgroups of patients with AS and nr-axSpA (Table 24). As noted in Section 6.1.3 (Subject Disposition) there were differences in the classification of patients into these subgroups based on whether the x-rays were evaluated centrally or locally. The efficacy results are displayed based on both methods of classification for the subgroups of patients with AS and nr-axSpA. When evaluating patients based on local x-ray interpretations, the magnitude of treatment effect was slightly larger for the patients with nr-axSpA than patients with AS at week 24. However, based on central x-ray interpretation, the magnitude of the treatment effect was almost the same for patients with AS and nr-axSpA. Overall, the results in the subgroups of patients with AS and nr-axSpA were consistent with the trends demonstrated in the overall population. We recognize that these subgroup analyses are exploratory and should be interpreted cautiously.

Reviewer's comments: In the overall population axial SpA population, there were statistically significant improvements in ASAS20 response proportions for patients treated with certolizumab. In general, similar trends were seen in the subgroup of patients with AS and nr-axSpA.

Table 24: ASAS20 responses at Week 12 and Week 24 in AS and nr-axSpA subgroups

	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W + CZP 400mg Q4W
LOCAL READ				
AS subgroup, local read, N	57	65	56	121
Week 12				
Responders (%)	37	57	64	60
Difference to PBO (%)	---	20*	27*	24*
Week 24				
Responders (%)	33	68	70	69
Difference to PBO (%)	---	34**	36**	35**
nr-axSpA subgroup, local read, N	50	46	51	97
Week 12				
Responders (%)	40	59	63	61
Difference to PBO (%)	---	19	23*	21*
Week 24				
Responders (%)	24	65	71	68.
Difference to PBO		41**	47**	44**
CENTRAL READ				
AS subgroup, central read, N	57	66	61	127
Week 12				
Responders (%)	46	61	69	65
Difference to PBO (%)	---	15	23*	19*
Week 24				
Responders (%)	32	65	74	69
Difference to PBO	---	34**	42**	38**
nr-axSpA subgroup, central read, N	35	33	30	63
Week 12				
Responders (%)	20	42	47	44
Difference to PBO (%)	---	22*	27*	24*
Week 24				
Responders (%)	17	61	53	57
Difference to PBO (%)	---	44**	36*	40**

*p<0.005, **p<0.001
AS=ankylosing spondylitis; ASAS20=Assessment in Axial Spondyloarthritis International Society 20% response criteria; CZP=certolizumab; –=not applicable; nr-axSpA=nonradiographic axial spondyloarthritis; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, tables 8-2 (page 140), 8-3 (142); Response to FDA information request, amendment dated 5/16/13 tables 1-2 (page 3) and 1-3 (4)

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary endpoints in trial AS001 were BASFI, BASDAI, and BASMI at 12 and 24 weeks. See Table 22 and Table 25 for definitions of these endpoints. Additional

endpoints of interest were the ASAS response components, ASAS40, ASAS5/6, partial remission, and BASDAI-50 responders, and BASDAI-fatigue and nocturnal back pain.

Table 25: The Bath AS Metrology Index (BASMI) and BASMI linear

Instrument	Definition	Range
Bath AS Metrology Index (BASMI)	Comprises the sum of 5 measures of hip and spine mobility [i.e. tragus-to-wall, lumbar flexion (Schober test), cervical rotation, lumbar side flexion, and intermalleolar distance] that are each categorized as 0 (mild), 1 (moderate), or 2 (severe)	0 to 10
BASMI linear	The same as BASMI, except the 5 measures are scored according to the BASMI linear definition (Table 13) and then the mean of the 5 scores is taken.	0 to 10

Source: FDA generated

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Components of axial spondyloarthritis disease activity in trial AS001

The ASAS20 response criteria are composed of the patient global assessment, total spine pain score, functional assessment (BASFI), and inflammation assessment (questions 5 and 6 of the BASDAI).

Table 26 displays the mean change from baseline at Weeks 12 and 24 in the 4 components of the ASAS response criteria in trial AS001. Treatment with certolizumab showed greater improvement in all 4 components of ASAS at Weeks 12 and 24. The results were consistent for the two doses of certolizumab: 200mg Q2W and 400mg Q4W.

Table 26: Change from baseline in ASAS components at Weeks 12 and 24 in overall axial SpA population (FAS)

	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W + CZP 400mg Q4W
Overall axial SpA population, N	106	111	107	218
Patient global assessment				
Week 12				
Difference to placebo, LS mean (SE)	---	-1.6 (0.4)	-1.8 (0.4)	-1.7 (0.3)
P-value	---	<0.001	<0.001	<0.001
Week 24				
Difference to placebo, LS mean (SE)	---	-2.4 (0.3)	-2.1 (0.3)	-2.2 (0.3)
P-value	---	<0.001	<0.001	<0.001
Total back pain				
Week 12				
Difference to placebo, LS mean (SE)	---	-1.7 (0.3)	-1.6 (0.3)	-1.6 (0.3)
P-value	---	<0.001	<0.001	<0.001
Week 24				
Difference to placebo, LS mean (SE)	---	-1.9 (0.3)	-1.9 (0.3)	-1.9 (0.3)
P-value	---	<0.001	<0.001	<0.001
Function (BASFI)				
Week 12				
Difference to placebo, LS mean (SE)	---	-1.5 (0.3)	-1.5 (0.3)	-1.5 (0.2)
P-value	---	<0.001	<0.001	<0.001
Week 24				
Difference to placebo, LS mean (SE)	---	-2.0 (0.3)	-1.8 (0.3)	-1.9 (0.3)
P-value	---	<0.001	<0.001	<0.001
Inflammation (BASDAI Q5/6)				
Week 12				
Difference to placebo, LS mean (SE)	--	-2.0 (0.3)	-2.0 (0.3)	-1.9 (0.3)
P-value	---	<0.001	<0.001	<0.001
Week 24				
Difference to placebo, LS mean (SE)	---	-2.3 (0.3)	-2.2 (0.3)	-2.3 (0.3)
P-value	---	<0.001	<0.001	<0.001

Patient global assessment ranges from 0=not active to 10=very active
Total back pain numerical rating scale (NRS) where 0=no pain and 10=most severe pain
BASFI is a functional index where 0=easy and 10=impossible
BASDAI Q5 is an NRS where 0=none and 10=most severe; **BASDAI Q6** is an NRS where 0=0 hours and 10=2 or more hours

CZP=certolizumab; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; FAS=full analysis set; LS=least square; SE=standard error
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, tables 8-4 (pages 144-5), 8-12 (166), 8-13 (168), 8-14 (170)

Table 27 displays the mean change from baseline at Weeks 12 and 24 in BASFI for the subgroups of patients AS and nr-axSpA. The BASFI is one component of the ASAS response criteria. These results are presented by both local and central x-ray classification. In general, the results for the subgroups of AS and nr-axSpA showed similar trends to those seen for the overall population regardless of whether subgroup classification was based on local or central x-ray interpretation. While the trends were similar regardless of whether x-rays were evaluated centrally or locally, the magnitude of the treatment difference was larger for the nr-axSpA subgroup based on local x-ray classification and was larger for the AS subgroup based on central x-ray classification. Similar trends were observed for BASDAI, but not BASMI. We recognize that these subgroup analyses are exploratory and should be interpreted cautiously.

Table 27: Change from baseline in BASFI at weeks 12 and 24 in AS and nr-axSpA subgroups based on local and central x-ray interpretation

BASFI	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W + CZP 400mg Q4W
LOCAL				
AS subgroup (N), local read	57	65	56	121
Week 12 difference to placebo, LS mean (SE)	---	-1.2 (0.4)*	-1.1 (0.4)*	-1.1 (0.3)**
Week 24 difference to placebo, LS mean (SE)	---	-1.6 (0.4)**	-1.6 (0.4)**	-1.6 (0.3)**
Nr-axSpA subgroup (N), local read	50	46	51	97
Week 12 difference to placebo, LS mean (SE)	---	-1.9 (0.4)**	-1.9 (0.4)**	-1.9 (0.4)**
Week 24 difference to placebo, LS mean (SE)	---	-2.4 (0.5)**	-2.1 (0.4)**	-2.2 (0.4)**
CENTRAL				
AS subgroup (N), central read	57	66	61	127
Week 12 difference to placebo, LS mean (SE)	---	-1.4 (0.4)**	-1.5 (0.4)**	-1.4 (0.3)**
Week 24 difference to placebo, LS mean (SE)	---	-2.1 (0.4)**	-2.2 (0.4)**	-2.2 (0.3)**
Nr-axSpA subgroup (N), central read	35	33	30	63
Week 12 difference to placebo, LS mean (SE)	---	-1.3 (0.5)*	-1.1 (0.5)*	-1.2 (0.4)*
Week 24 difference to placebo, LS mean (SE)	---	-1.7 (0.6)*	-1.0 (0.6)	-1.4 (0.5)*

*p<0.05, **p<0.001
BASFI is a functional index where 0=easy and 10=impossible
AS=ankylosing spondylitis; nr-axSpA=nonradiographic axial spondyloarthritis; CZP=certolizumab; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; LS=least square; SE=standard error
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, tables 8-4, pages 144-5; Response to FDA information request, amendment dated 5/16/13, tables 1-4 (page 5-6)

ASAS40, ASAS5/6, partial remission, BASDAI-50 responses

Table 28 displays the proportion of patients with secondary dichotomous endpoints at Week 12 and Week 24 in the overall axial SpA population. In the overall population, a greater proportion of patients in the certolizumab 200mg Q2W and 400mg Q4W groups, compared to the placebo group, had ASAS40, ASAS5/6, partial remission, and BASDAI-50 responses at Weeks 12 and 24.

Table 28: ASAS40, ASAS5/6, partial remission, and BASDAI-50 responses at Week 12 and Week 24 in overall axial SpA population (FAS)

Responders (%)	PBO %	CZP 200mg Q2W %	CZP 400mg Q4W %	CZP 200mg Q2W + CZP 400mg Q4W %
Overall axial SpA population, N	106	111	107	218
Week 12 **ASAS40**	18	43	49	46
Difference to placebo	---	25**	31**	28**
Week 24 **ASAS40**	15	51	52	52
Difference to placebo	---	36**	37**	37**
Week 12 **ASAS5/6**	9	45	41	43
Difference to placebo	---	37**	33**	35**
Week 24 **ASAS5/6**	5	37	48	42
Difference to placebo	---	32**	43**	38**
Week 12 **partial remission**	4	23	24	24
Difference to placebo	---	20**	21**	20**
Week 24 **partial remission**	9	31	30	30
Difference to placebo	---	22**	21**	22**
Week 12 **BASDAI-50**	13	45	44	45
Difference to placebo	---	32**	31**	31**
Week 24 **BASDAI-50**	18	51	54	52
Difference to placebo	---	33**	36**	34**

ASAS40 is improvements of at least 40% and absolute improvement of at least 2 unites on a 0 to 10 numerical rating scale (NRS) in at least 3 of the following 4 domains (and no worsening in the remaining domains): patient global assessment, pain, function (BASFI), and inflammation (from BASDAI)
ASAS5/6 responders achieved a 20% improvement from baseline in 5 of the following 6 domains: total back pain (VAS 0 to 10cm), patent global (VAS 0 to 10cm), function (BASFI score), the mean morning stiffness score in the BASDAI (VAS 0 to 10cm), CRP, and spine mobility (lumbar side flexion)
Partial remission is achieved by a score of ≤2 units on a 0 to 10 unit scale in all 4 domains in the ASAS response (patient global, total back pain, BASFI, and BASDAI)
BASDAI-50 responders achieved at least a 50% improvement in the 0-10 BASDAI score. The BASDAI contains 6 patient-reported outcomes (i.e., fatigue, spinal pain, joint pain, enthesitis, overall level of morning stiffness, and duration of morning stiffness), each on a 0-10 scale. The first 4 scales are weighted by 0.2 and the last two are weighted by 0.1 to produce a BASDAI range of 0-10.
Axial SpA=axial spondyloarthritis; PBO=placebo; CZP=certolizumab; Q2W=every 2 weeks; Q4W=every 4 weeks; FAS=full analysis set
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, tables 8-3 (page 158), 8-10 (160-1), 8-11 (164-5), 8-17 (178)

BASDAI, BASDAI-fatigue, and nocturnal back pain

Table 29 displays the mean changes from baseline in BASDAI, BASDAI-fatigue, and nocturnal back pain at Week 12 and Week 24 in the overall axial SpA population. The mean changes in these parameters in patients treated either dose of certolizumab were significantly higher than the placebo group at Weeks 12 and 24. There was no clear relationship between the magnitude of the treatment effect and the dose of certolizumab.

Table 29: Change from baseline in BASDAI, BASDAI-fatigue, and nocturnal back pain at Weeks 12 and 24 in overall axial SpA population (RS and FAS)

	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W + CZP 400mg Q4W
Overall axial SpA population, N	106	111	107	218
BASDAI-fatigue				
Week 12				
Difference to placebo, LS mean (SE)	---	-1.3 (0.3)	-1.2 (0.3)	-1.3 (0.3)
P-value	---	<0.001	<0.001	<0.001
Week 24				
Difference to placebo, LS mean (SE)	---	-1.7 (0.3)	-1.8 (0.3)	-1.7 (0.3)
P-value	---	<0.001	<0.001	<0.001
Overall axSpA population, N	107	111	107	218
BASDAI				
Week 12				
Difference to placebo, LS mean (SE)	---	-1.6 (0.3)	-1.6 (0.3)	-1.6 (0.2)
P-value	---	<0.001	<0.001	<0.001
Week 24				
Difference to placebo, LS mean (SE)	---	-2.0 (0.3)	-2.0 (0.3)	-2.0 (0.3)
P-value	---	<0.001	<0.001	<0.001
Overall axSpA population, N	106	111	107	218
Nocturnal back pain				
Week 12				
Difference to placebo, LS mean (SE)	---	-1.8 (0.4)	-1.9 (0.4)	-1.8 (0.3)
P-value	---	<0.001	<0.001	<0.001
Week 24				
Difference to placebo, LS mean (SE)	---	-2.3 (0.4)	-2.3 (0.4)	-2.3 (0.3)
P-value	---	<0.001	<0.001	<0.001

Fatigue was assessed via question 1 of the BASDAI, which is a numerical rating scale (NRS) for an overall level of fatigue/tiredness where 0=none and 10=very severe.
BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; contains 6 patient-reported outcomes (i.e. fatigue, spinal pain, joint pain, enthesitis, overall level of morning stiffness, and duration of morning stiffness), each on a 0-10 scale. The first 4 scales are weighted by 0.2 and the last two are weighted by 0.1 to produce a BASDAI range of 0-10.
Nocturnal pain was assessed with a 0 to 10 scale with 0 indicating no pain and 10 indicating most severe pain
CZP=certolizumab; axSpA=axial spondyloarthritis; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; FAS=full analysis set; LS=least squares; SE=standard error
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, tables 8-5 (pages 147-8), 8-19 (180), 8-15 (173)

Table 30 displays the mean change from baseline in BASDAI in the subgroups of patients with nr-axSpA and AS according to central and local x-ray classification. In general, the BASDAI results for the AS and nr-axSpA subgroups showed similar trends to those seen for the overall population regardless of whether the subgroup classification was based on local or central x-ray interpretation. While the trends were similar regardless of whether x-rays were evaluated centrally or locally, the magnitude of the treatment difference depended on whether x-rays were evaluated locally or centrally. The treatment difference was larger for the nr-axSpA subgroup based on local x-ray classification, but was smaller for the nr-axSpA subgroup based on central x-ray classification. Similar trends were observed for BASFI, but not BASMI. We recognize that these subgroup analyses are exploratory and should be interpreted cautiously.

Table 30: Change from baseline in BASDAI at Weeks 12 and 24 in AS and nr-axSpA subgroups

BASDAI	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W + CZP 400mg Q4W
LOCAL				
AS subgroup (N), local read	57	65	56	121
Week 12 difference to placebo, LS mean (SE)	---	-1.5 (0.4)**	-1.4 (0.4)**	-1.5 (0.3)**
Week 24 difference to placebo, LS mean (SE)	---	-1.9 (0.4)**	-1.9 (0.4)**	-1.9 (0.3)**
Nr-axSpA subgroup (N), local read	50	46	51	97
Week 12 difference to placebo, LS mean (SE)	---	-1.8 (0.4)**	-1.9 (0.4)**	-1.8 (0.4)**
Week 24 difference to placebo, LS mean (SE)	---	-2.3 (0.5)**	-2.2 (0.5)**	-2.2 (0.4)**
CENTRAL				
AS subgroup (N), central read	57	66	61	127
Week 12 difference to placebo, LS mean (SE)	---	-1.7 (0.4)**	-1.8 (0.4)**	-1.7 (0.3)**
Week 24 difference to placebo, LS mean (SE)	---	-2.3 (0.4)**	-2.4 (0.4)**	-2.3 (0.3)**
Nr-axSpA subgroup (N), central read	35	33	30	63
Week 12 difference to placebo, LS mean (SE)	---	-1.2 (0.5)*	-1.0 (0.6)	-1.1 (0.5)*
Week 24 difference to placebo, LS mean (SE)	---	-1.8 (0.6)*	-1.4 (0.6)*	-1.6 (0.5)*

*p<0.05, **p<0.001
BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; contains 6 patient-reported outcomes (i.e. fatigue, spinal pain, joint pain, enthesitis, overall level of morning stiffness, and duration of morning stiffness), each on a 0-10 scale. The first 4 scales are weighted by 0.2 and the last two are weighted by 0.1 to produce a BASDAI range of 0-10.
AS=ankylosing spondylitis; CZP=certolizumab; nr-axSpA=nonradiographic axial spondyloarthritis; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; LS=least square; SE=standard error
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, tables 8-5 (pages 147-8), 4.34.2 (2051-62), 4.32.2 (1846-56), 4.32.3 (1857-67); Response to FDA information request, amendment dated 5/16/13, table 1-5 (7-8)

Spinal Mobility

Spinal mobility was assessed by the BASMI at Baseline, Week 12, and Week 24. Statistically significant differences in certolizumab-treated patients compared with placebo-treated patients were demonstrated at each post-baseline visit in the overall axial SpA population (Table 31). The difference to placebo in mean change from baseline in BASMI linear at Week 12 was -0.40 points in the certolizumab-treated patients (p<0.001) and -0.44 points (p<0.001) at Week 24.

Table 31: Change from baseline in BASMI linear at Weeks 12 and 24 in overall axial SpA population (RS)

BASMI linear	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W + CZP 400mg Q4W
Overall axSpA population, N	107	111	107	218
Week 12				
Change from Baseline, LS mean (SE)	-0.1 (0.1)	-0.6 (0.1)	-0.5 (0.1)	-0.5 (0.1)
Difference to placebo, LS mean (SE)	---	-0.5 (0.1)	-0.3 (0.1)	-0.4 (0.1)
P-value	---	<0.001	0.005	<0.001
Week 24				
Change from Baseline, LS mean (SE)	-0.1 (0.1)	-0.5 (0.1)	-0.5 (0.1)	-0.5 (0.1)
Difference to placebo, LS mean (SE)	---	-0.5 (0.1)	-0.4 (0.1)	-0.4 (0.1)
P-value	---	<0.001	<0.001	<0.001

BASMI=Bath Ankylosing Spondylitis Functional Metrology Index; comprises of the sum of 5 measures of hip and spine mobility [i.e., tragus-to-wall, lumbar flexion (Schober test), cervical rotation, lumbar side flexion, and intermalleolar distance] that are each categorized as 0 (mild), 1 (moderate), or 2 (severe). The BASMI ranges from 0-10. For the BASMI linear the 5 measures are scored according to the BASMI linear definition (Table 13) and then the mean of the 5 scores is taken.
CZP=certolizumab; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; LS=least square; SE=standard error; axial SpA=axial spondyloarthritis
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 8-6, pages 150-1

Compared to the overall population, similar results were noted in the AS and nr-axSpA subgroups regardless method of x-ray classification (Table 32). When comparing treatment difference between the subgroups, the treatment difference was slightly larger in the nr-axSpA subgroup, than the AS subgroup based on local x-ray interpretation. Based on central x-ray interpretation, the treatment difference was similar in the nr-axSpA and AS subgroups. We recognize that these subgroup analyses are exploratory and should be interpreted cautiously.

Table 32: Change from baseline in BASMI linear at Weeks 12 and 24 in AS and nr-axSpA subgroups (RS)

BASMI linear	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W + CZP 400mg Q4W
LOCAL				
AS subgroup (N), local read	57	65	56	121
Week 12				
Change from Baseline, LS mean (SE)	-0.2 (0.1)	-0.6 (0.1)	-0.3 (0.2)	-0.5 (0.1)
Difference to placebo, LS mean (SE)	---	-0.3 (0.2)	-0.1 (0.2)	-0.2 (0.2)
Week 24				
Change from Baseline, LS mean (SE)	-0.3 (0.1)	-0.6 (0.2)	-0.6 (0.2)	-0.6 (0.1)
Difference to placebo, LS mean (SE)	---	-0.4 (0.2)*	-0.3 (0.2)	-0.3 (0.2)*
Nr-axSpA subgroup (N), local read	50	46	51	97
Week 12				
Change from Baseline, LS mean (SE)	0.02 (0.1)	-0.6 (0.2)	-0.5 (0.2)	-0.6 (0.1)
Difference to placebo, LS mean (SE)	---	0.6 (0.2)**	-0.6 (0.2)**	-0.6 (0.1)**
Week 24				
Change from Baseline, LS mean (SE)	0.1 (0.2)	-0.5 (0.2)	-0.4 (0.2)	-0.4 (0.2)
Difference to placebo, LS mean (SE)	---	-0.6 (0.2)**	-0.6 (0.2)*	-0.6 (0.2)**
CENTRAL				
AS subgroup (N), central read	57	66	61	127
Week 12				
Change from Baseline, LS mean (SE)	-0.1 (0.8)	-0.6 (1.0)	-0.5 (0.7)	-0.5 (0.9)
Difference to placebo, LS mean (SE)	---	-0.6 (0.2)**	-0.4 (0.2)*	-0.5 (0.1)**
Week 24				
Change from Baseline, LS mean (SE)	-0.2 (0.9)	-0.6 (1.1)	-0.7 (0.8)	-0.6 (1.0)
Difference to placebo, LS mean (SE)	---	-0.5 (0.2)*	-0.5 (0.2)*	-0.5 (0.2)*
Nr-axSpA subgroup (N), central read	35	33	30	63
Week 12				
Change from Baseline, LS mean (SE)	0.04 (0.9)	-0.4 (0.8)	-0.3 (1.0)	-0.4 (0.9)
Difference to placebo, LS mean (SE)	---	-0.5 (0.2)*	-0.5 (0.2)	-0.5 (0.2)*
Week 24				
Change from Baseline, LS mean (SE)	0.1 (0.9)	-0.5 (1.0)	-0.3 (1.0)	-0.4 (1.0)
Difference to placebo, LS mean (SE)	---	-0.6 (0.2)*	-0.4 (0.2)	-0.5 (0.2)*

*p<0.05, **p<0.001
BASMI=Bath Ankylosing Spondylitis Functional Metrology Index; comprises of the sum of 5 measures of hip and spine mobility [i.e., tragus-to-wall, lumbar flexion (Schober test), cervical rotation, lumbar side flexion, and intermalleolar distance] that are each categorized as 0 (mild), 1 (moderate), or 2 (severe). The BASMI ranges from 0-10. For the BASMI linear the 5 measures are scored according to the BASMI linear definition (Table 13) and then the mean of the 5 scores is taken.
AS=ankylosing spondylitis; CZP=certolizumab; nr-axSpA=nonradiographic axial spondyloarthritis; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; LS=least square; SE=standard error
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 8-6, pages 150-1; Response to FDA information request, amendment dated 5/16/13, table 1-6, pages 9-10

6.1.6 Other Endpoints

No additional endpoints were evaluated in this clinical review. Please see the statistical review for additional discussion of other endpoints.

6.1.7 Subpopulations

See Section 6.1.5 (Analysis of Secondary Endpoints) for a discussion of the efficacy results in the subgroups of patients with AS and nr-axSpA.

Table 33 displays subgroup efficacy analyses, using the primary efficacy endpoint (ASAS20 response at Week 12), by demographic and disease characteristics in trial AS001. While there was some variation in the magnitude of the treatment effect in the various subgroups, there did not appear to be noticeable interactions between treatment group and these factors. However, there appeared to be a trend toward a greater magnitude of effect in patients with higher CRP levels and male gender.

Table 33: ASAS20 response at Week 12 by subgroups (RS)

Difference from placebo in percentage of responders	PBO	CZP 200mg Q2W % difference from placebo	CZP 400mg Q4W % difference from placebo	p-value for interaction
Age at baseline				0.94
<45 years	---	17	24	
≥45 years	---	19	28	
Gender				0.22
Female	---	5	21	
Male	---	29	28	
Symptom duration				0.98
<5 years	---	18	24	
≥5 years	---	21	26	
Baseline CRP category				0.43
≤15mg/L	---	13	25*	
>15mg/L	---	29*	25*	
Region				0.98
EU	---	18	24	
America	---	21	27	

CZP=certolizumab; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set, CRP=c-reactive protein
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 8-28, pages 196-7

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Sponsor studied two treatment regimens in their one Phase 3 trial in axial SpA: certolizumab 200mg Q2W and certolizumab 400mg Q4W. The cumulative doses administered over time were the same for both treatment groups. These doses were selected based on certolizumab's demonstrated therapeutic efficacy in previous studies in RA. The two studied doses had a similar magnitude of treatment effect on the primary and secondary endpoints.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Sponsor submitted 24 weeks of placebo controlled data to support the efficacy of certolizumab for the treatment of axial SpA. The endpoints were evaluated at 12 and 24 weeks. The data at 24 weeks suggest sustained improvement to that achieved after 12 weeks of certolizumab treatment. There was no evidence of drug tolerance.

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues or analyses were performed as part of this clinical review.

7 Review of Safety

Safety Summary

The safety information for certolizumab in axial SpA is obtained from one trial during which 274 patients received at least one dose of certolizumab. The Sponsor submitted data from the 24-week double-blind period. The median treatment duration was 20 weeks (range 4 to 25 weeks). Following the 24-week double-blind period, there was an ongoing 110-week open label extension. However, the primary safety analyses are derived from the completed 24-week double-blind treatment period.

There were no deaths during the 24-week, double-blind treatment period.

Serious adverse events (SAEs) were uncommon during the 24-week, double-blind treatment period. The proportion of patients with SAEs was balanced between the overall certolizumab group and the placebo group (5% for each). No SAEs were reported in more than one patient. A slightly higher percentage of patients treated with certolizumab 400mg Q4W had SAEs compared to the placebo and certolizumab 200mg Q2W groups. The percentage of patients with SAEs in the system organ class (SOC) hepatobiliary disorders and infections and infestations was slightly higher in the patients treated with certolizumab than placebo.

The proportion of patients with adverse events (AEs) leading to discontinuation was balanced between the placebo and certolizumab groups. A slightly higher proportion of patients in the certolizumab group compared to the placebo group had AEs. The most common AEs in the certolizumab-treatment group were nasopharyngitis (9%), headache (6%), blood creatine phosphokinase increased (5%), and rash (4%). All of these AEs were more common in the certolizumab-treatment group than the placebo-treatment group, except for headache.

Due to specific safety concerns with TNF-inhibitors, analyses were conducted related to AEs of special interest, including infections, malignancies, hepatotoxicity, cardiovascular events, demyelinating disorders, injection site reactions, autoimmunity, and hematologic

cytopenias. These analyses did not reveal new safety concerns with the use of certolizumab in axial SpA.

Overall, no new safety signals were identified in Trial AS001 and certolizumab had a similar safety profile in axial SpA compared to the safety profile reflected in the product label. While no new safety signals were identified in Trial AS001, the safety profile of certolizumab is well-characterized for RA patients and the known risks of certolizumab should be considered in the risk/benefit consideration.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See Section 5.2 (Review Strategy) for the trial used to evaluate the safety of certolizumab in the treatment of axial spondyloarthritis. See Table 7 for the design of the trial in axial spondyloarthritis.

7.1.2 Categorization of Adverse Events

The Sponsor's categorization of adverse events with preferred terms are consistent with the investigator's verbatim terms including the most common adverse events leading to discontinuation.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In this sBLA review, pooling is not performed across studies because only one trial in axial spondyloarthritis was submitted in support of the safety and efficacy of certolizumab for this indication. The Sponsor provides the following definitions of populations analyzed for safety analyses:

- **Safety analysis set**: All patients in the randomized set who received at least one dose of trial medication. The randomized set consisted of all patient randomized into the trial with an intention to treat.

The Sponsor also performed analyses in the subgroup of patients with AS based on local x-ray interpretation. At the request of the FDA, the Sponsor performed additional subgroup analyses based on central x-ray interpretation. Given limitations to analyzing safety data in subgroups, including small number of patients and the *post-hoc* nature of the analyses, these safety analyses will not be reviewed in this document. The focus of this review is on safety analyses performed using the safety analysis set. Safety analyses in the AS subgroup will be mentioned for completeness as appropriate.

7.2 Adequacy of Safety Assessments

In the safety database from the one complete trial of certolizumab, 274 patients received at least one dose of certolizumab. The Sponsor calculated the median duration of exposure in a "narrow sense" and a "broader sense." A narrow sense was defined as the last injection date minus the first injection date plus 14 days (if receiving certolizumab every 2 weeks) or 28 days (if receiving certolizumab every 4 weeks). A broader sense was defined as the last injection date minus the first injection date plus 70 days. Safety data for the certolizumab treated patients who escaped to placebo were not included in the placebo group after escape; but rather were presented according to the dose of certolizumab to which they escaped. Thus, patients may have been counted more than once. The Sponsor defined the "all certolizumab" group as patients who were randomized to either dose of certolizumab or escaped from placebo to certolizumab. This is a reasonable manner in which to analyze safety data.

Table 34 displays the extent of exposure to certolizumab in the one Phase 3 trial by duration as of the last safety cut-off date.

The extent of exposure is similar to previous safety databases used to support approval for the indication of AS (Table 35). However, it is unclear if this safety database is adequate for the expanded indication "axial spondyloarthritis."

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Table 34: Extent of Exposure (Safety Set)

	Placebo†	CZP 200mg Q2W	CZP 400mg Q4W	All CZP‡
N	107	111	107	274
Patient-years of exposure	38.9	55.5	53.3	108.8
Number of doses received§				
Mean	8.9 (2.7)	11.4 (1.5)	6.7 (1.0)	7.9 (3.3)
Median	8.0	12.0	7.0	7.0
Min, max	1, 12	3, 12	1, 7	1, 12
Duration of exposure in narrow sense‖ (weeks)				
Mean	18.2 (5.6)	23.3 (2.6)	23.3 (3.4)	20.2 (6.8)
Median	16.1	24.0	24.0	24.0
Min, max	2, 26	10, 25	4, 25	4, 25
Duration of exposure in broad sense (weeks)¶				
Mean	19 (4.4)	23.7 (1.3)	23.8 (2.5)	20.6 (6.5)
Median	16.1	24.0	24.0	24.0
Min, max	10, 26	16, 26	10, 31	7, 31

†=For the entire placebo group, placebo exposure will end with the date of first CZP injection for subjects escaping from placebo to CZP; ‡=includes CZP 200mg Q2W, CZP 400mg Q4W, and the escaped placebo subjects with their CZP data; §=dose days (placebo injection days for the 400mg Q4W group were not counted); ‖=last injection date-first injection date+14 (28) days; ¶ last injection date-first injection date+70 days
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 11-1, page 225

Table 35: Comparison of number of patients studied in different clinical development programs for AS and nr-axSpA development programs

Drug (indication)	Total N=	Dose 1 N=	Dose 2 N=	Placebo N=
Golimumab (AS)	356	138	140	78
Infliximab (AS)	279	201	--	78
Etanercept (AS)	277	138	--	139
Adalimumab (AS)	315	208	--	107
Adalimumab (nr-axSpA)†	185	94	--	91
Certolizumab†				
Total with spondyloarthritis	325	111	107	107
AS	178	65	56	57
nr-axSpA	147	46	51	50

† supplemental biologics license application under review
AS=ankylosing spondylitis; nr-axSpA=nonradiographic axial spondyloarthritis
Source: FDA generated from publically available prescribing information, accessed May 20, 2013

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

See Section 6.1.2 (Demographics) for the baseline demographics in the controlled trial in axial SpA. It is unclear if the baseline demographics in axial SpA are typical of all patients with axial SpA given the limited epidemiological information available. The baseline demographics in the subgroup of patients with AS was typical of AS patients.

There was adequate certolizumab exposure to perform subgroup safety analyses by gender [see Section 7.5.3 (Drug-demographic Interactions)].

7.2.2 Explorations for Dose Response

No data are available regarding potential dose-dependency for adverse events in patients with axial SpA. Specifically, the one trial in patients with axial SpA used two doses of certolizumab, however they have similar drug exposure. The Sponsor noted that dose-ranging was not performed in axial SpA due to the availability of risk/benefit data in other indications. Specifically, previous dose-ranging studies in RA have suggested a favorable risk/benefit ratio for the two chosen doses. Thus, additional doses were not available. Similar strategies have been utilized in other programs in AS.

Reviewer's comments: It is unclear whether it is possible to extrapolate safety and efficacy data from conventional dose-ranging in other rheumatic disease indications to the new indication, axial SpA.

7.2.3 Routine Clinical Testing

Table 36 displays a summary of the clinical testing that was performed in the trial AS001 to elicit AEs, vital signs, laboratory parameters, and other safety information. The types and frequencies of safety tests used to assess AEs, vital signs, labs, and other tests were adequate to assess the safety of certolizumab in axial spondyloarthritis. These safety tests were adequate to evaluate the known TNF-inhibitor associated AEs.

Table 36: Clinical testing to elicit AEs, vital signs, and laboratory parameters in trial M10-791

Evaluation	Frequency
AE review	Every visit which occurred at least every 2 weeks
Physical examination	Screening, Baseline, Weeks 1, 2, 4, 8, 12, 16, 18, 20, 24, Early Withdrawal, and SFU
CXR	Screening chest x-ray must have occurred within 3 months prior to Screening Visit and repeated at Weeks 48, 96, and 158 only.
TB testing	Screening and Weeks 48 and 96.
Laboratory analyses (hematology, biochemistry, urinalysis, and CRP)	Screening, Baseline, Weeks 1, 2, 4, 8, 12, 16, 18, 20, 24, Early Withdrawal, and SFU
AP pelvis x-ray	Baseline for all subjects randomized after implementation of Amendment 1 at the site. A sacroiliac joint x-ray performed ≤12 weeks prior to the Baseline Visit could be used as the Baseline assessment provided that the film could be submitted and met the requirements for central reading.
Spine x-ray and MRI	At selected sites only, spine x-rays were performed at Baseline, Week 12, Week 96, and at withdrawal if subject withdraws prior to Week 96. Magnetic resonance imaging was performed at Baseline, Week 12, Week 48, Week 96, and at withdrawal if subject withdraws prior to Week 96.
Vital signs	Screening, Baseline, Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, Early Withdrawal, and SFU.

CXR=chest x-ray; TB=tuberculosis; MRI=magnetic resonance imaging; SFU=safety follow-up
Source: FDA generated

7.2.4 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Trial AS001 incorporated monitoring for toxicities associated with TNF-inhibitors, such as infections, hepatotoxicity, and injection site reactions. Details of these analyses are found in Section 7.3.4 (Submission Specific Primary Safety Concerns).

7.3 Major Safety Results

7.3.1 Deaths

In trial AS001, there were no deaths during the 24 week trial.

7.3.2 Nonfatal Serious Adverse Events

In trial AS001, serious adverse events were defined as any adverse event that resulted in death, was life-threatening, resulted in significant or persistent disability/incapacity, caused congenital anomaly/birth defect, was an important medical event that, based upon appropriate medical judgment, may have jeopardized the patient or subject and

may have required medical or surgical intervention to prevent one of the other outcomes considered serious, or resulted in hospitalization or prolongation of hospitalization.

Table 37 displays the SAEs in trial AS001 through Week 24. The same proportion of patients in the overall certolizumab group and the placebo group had SAEs (both 4.7%). No SAEs were reported in more than 1 patient. A slightly higher percentage of patients treated with certolizumab 400mg Q4W had SAEs compared to the placebo and certolizumab 200mg Q2W groups.

Notably, the percentage of patients with hepatobiliary disorders and infections and infestations was slightly higher in the patients treated with certolizumab than placebo. SAEs related to hepatotoxicity and infections are discussed in Submission Specific Primary Safety Concerns (Section 7.3.5).

SAEs in the AS subpopulation were similar to the overall population.

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Table 37: Serious adverse events by system organ class and MedDRA preferred term in trial AS001 through Week 24 (Safety Set)

System organ class Preferred term	Placebo† n (%)	CZP 200mg Q2W n (%)	CZP 400mg Q4W n (%)	All CZP‡ n (%)
N	107	111	107	274
Any SAE	5 (4.7)	4 (3.6)	7 (6.5)	13 (4.7)
Blood and lymphatic system	0	1 (0.9)	0	1 (0.4)
Lymphadenopathy	0	1 (0.9)	0	1 (0.4)
Cardiac disorders	0	0	1 (0.9)	1 (0.4)
Supraventricular tachycardia	0	0	1 (0.9)	1 (0.4)
Eye disorders	0	1 (0.9)	0	1 (0.4)
Retinal vein occlusion	0	1 (0.9)	0	1 (0.4)
Gastrointestinal disorders	1 (0.9)	0	1 (0.9)	1 (0.4)
Abdominal pain	0	0	1 (0.9)	1 (0.4)
Inflammatory bowel disease	1 (0.9)	0	0	0
General disorders and administration site conditions	2 (1.9)	0	0	0
Non-cardiac chest pain	2 (1.9)	0	0	0
Hepatobiliary disorders	0	0	2 (1.9)	2 (0.7)
Cholelithiasis	0	0	1 (0.9)	1 (0.4)
Cholelithiasis migration	0	0	1 (0.9)	1 (0.4)
Immune system disorders	1 (0.9)	0	1 (0.9)	1 (0.4)
Hypersensitivity	0	0	1 (0.9)	1 (0.4)
Drug hypersensitivity	1 (0.9)	0	0	0
Infections and infestations	0	2 (1.8)	0	3 (1.1)
Appendicitis	0	0	0	1 (0.4)
Esophageal candidiasis	0	1 (0.9)	0	1 (0.4)
Haemophilus infection	0	1 (0.9)	0	1 (0.4)
Laryngitis	0	1 (0.9)	0	1 (0.4)
Investigations	0	1 (0.9)	0	1 (0.4)
Gamma-glutamylltransferase increased	0	1 (0.9)	0	1 (0.4)
Metabolism and nutrition disorders	0	0	0	1 (0.4)
Hypoglycemia	0	0	0	1 (0.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	1 (0.9)	1 (0.4)
Morton's neuroma	0	0	1 (0.9)	1 (0.4)
Renal and urinary disorders	1 (0.9)	0	1 (0.9)	1 (0.4)
Calculus ureteric	1 (0.9)	0	0	0
Renal colic	0	0	1 (0.9)	1 (0.4)
Respiratory, thoracic, and mediastinal disorders	0	0	1 (0.9)	1 (0.4)
Nasal polyps	0	0	1 (0.9)	1 (0.4)

CZP=certolizumab; PBO=placebo; AE=adverse event
†=entire placebo group, CZP data from placebo subjects were not utilized; ‡=includes CZP 200mg, CZP 400mg, and the escaped placebo subjects with their CZP data
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 11-6, page 232-3

7.3.3 Dropouts and/or Discontinuations

Table 38 displays the adverse events leading to discontinuation in trial AS001 through Week 24.

Overall, a small proportion of patients discontinued from the trial due to adverse events (1.8 to 3.7% in each certolizumab treatment group). The proportion of patients in the placebo group and the certolizumab 200mg Q2W group who discontinued secondary to adverse events was similar. A slightly lower proportion of patients in the certolizumab 200mg Q2W group compared to the certolizumab 400mg Q4W groups discontinued secondary to adverse events.

Notably a higher proportion of patients discontinued due to AEs in the system organ class of infections and infestations for the certolizumab 200mg Q2W group compared to the placebo group. These discontinuations secondary to AEs may be certolizumab related given the association of TNF-inhibitors and an increased incidence of infections.

Table 38: Discontinuations secondary to adverse events by system organ class and MedDRA preferred term in trial AS001 through Week 24 in overall population (Safety Set)

System organ class Preferred term	Placebo† n (%)	CZP 200mg Q2W n (%)	CZP 400mg Q4W n (%)	All CZP‡ n (%)
N	107	111	107	274
Any AE leading to permanent study medication discontinuation	2 (1.9)	2 (1.8)	4 (3.7)	6 (2.2)
General disorders and administration site conditions	1 (0.9)	0	0	0
Non-cardiac chest pain	1 (0.9)	0	0	0
Hepatobiliary disorders	1 (0.9)	0	1 (0.9)	1 (0.4)
Cholelithiasis	0	0	1 (0.9)	1 (0.4)
Hepatitis	1 (0.9)	0	0	0
Immune system disorders	0	0	1 (0.9)	1 (0.4)
Hypersensitivity	0	0	1 (0.9)	1 (0.4)
Infections and infestations	0	2 (1.8)	0	2 (0.7)
Folliculitis	0	1 (0.9)	0	1 (0.4)
Upper respiratory tract infection	0	1 (0.9)	0	1 (0.4)
Investigations	0	0	1 (0.9)	1 (0.4)
C-reactive protein increased§	0	0	1 (0.9)	1 (0.4)
Reproductive system and breast disorders	0	0	1 (0.9)	1 (0.4)
Gynecomastia	0	0	1 (0.9)	1 (0.4)

CZP=certolizumab; PBO=placebo; AE=adverse event
†=entire placebo group, CZP data from placebo subjects were not utilized; ‡=includes CZP 200mg, CZP 400mg, and the escaped placebo subjects with their CZP data; §=this event was reported at the subject's Early Termination Visit
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 11-7, page 234

7.3.4 Significant Adverse Events

AEs of interest for this product are discussed in Section 7.3.5 (Submission Specific Primary Safety Concerns). AEs leading to discontinuation are discussed in Section 7.3.3.

7.3.5 Submission Specific Primary Safety Concerns

Due to specific safety concerns with TNF-inhibitors, the Sponsor conducted analyses of adverse events related to infections, malignancies, hepatotoxicity, cardiovascular events, demyelinating disorders, injection site reactions, autoimmune disorders, hematologic cytopenias, and other events of interest.

Infections
More patients in the combined certolizumab group had AEs in the infections and infestations system organ class (SOC) (34.7%) than in the placebo group (23.4%). Most patients with an AE in the infections and infestations SOC reported events with maximum intensity of mild or moderate. No patients in the placebo group or certolizumab 400mg Q4W group had SAEs in the infection SOC. More patients in the certolizumab 200mg Q2W group had a serious infection (1.8%) compared to the certolizumab 400mg Q4W and placebo groups (0% for both) (Table 39). The serious infections occurred in three patients, two in the certolizumab 200mg Q2W group and one in a placebo patient who escaped to certolizumab 200mg Q2W. These serious events included appendicitis, esophageal candidiasis, haemophilus infection, and laryngitis.

The most common infection and infestation AE were in the high level term upper respiratory tract infection, which were reported with a higher percentage in the all certolizumab group than the placebo group (18.6% versus 12.1%). In addition to upper respiratory tract infection, herpes viral infections were more common in patients treated with certolizumab than placebo (1.8% versus 0%). All of the cases of herpes were oral herpes.

There were no rare or opportunistic infections.

There were no reported cases of active tuberculosis in the original submission. In the 120-day safety update, one confirmed case of active tuberculosis was reported in Latin America. The patient was permanently withdrawn from the study due to the AE. Tuberculosis is a known risk factor with TNF-inhibitors.

Table 39: Summary of adverse events in the infections and infestations system organ class during the 24-Week double blind treatment period (Safety Set)

	Placebo† n (%)	CZP 200mg Q2W n (%)	CZP 400mg Q4W n (%)	All CZP‡ n (%)
N	107	111	107	274
Any AE in infections and infestations SOC	25 (23.4)	43 (38.7)	41 (38.3)	95 (34.7)
Severe AE	0	0	0	1 (0.4)
Serious AE	0	2 (1.8)	0	3 (1.1)
Discontinuation due to AE	2 (1.9)	2 (1.8)	0	2 (0.7)

CZP=certolizumab; PBO=placebo; AE=adverse event; SOC=system organ class
†=entire placebo group, CZP data from placebo subjects were not utilized; ‡=includes CZP 200mg, CZP 400mg, and the escaped placebo subjects with their CZP data; §=this event was reported at the subject's Early Termination Visit
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 11-9, page 236

Table 40: Common adverse events in the infections and infestations disorders system organ class, occurring in ≥1.5% of patients in any group during the 24-week double blind treatment period (Safety Set)

Preferred term	Placebo† n (%)	CZP 200mg Q2W n (%)	CZP 400mg Q4W n (%)	All CZP‡ n (%)
N	107	111	107	274
Any AE in the Infections and Infestations SOC	25 (23.4)	43 (38.7)	41 (38.3)	95 (34.7)
Nasopharyngitis	7 (6.5)	11 (9.9)	11 (10.3)	24 (8.8)
Upper respiratory tract infection	3 (2.8)	6 (5.4)	4 (3.7)	11 (4.0)
Pharyngitis	1 (0.9)	5 (4.5)	1 (0.9)	7 (2.6)
Urinary tract infection	4 (3.7)	2 (1.8)	3 (2.8)	7 (2.6)
Cystitis	1 (0.9)	0	2 (1.9)	3 (1.1)
Folliculitis	0	3 (2.7)	2 (1.9)	6 (2.2)
Bronchitis	1 (0.9)	4 (3.6)	1 (0.9)	6 (2.2)
Oral herpes	0	3 (2.7)	2 (1.9)	5 (1.8)
Influenza	2 (1.9)	1 (0.9)	4 (3.7)	5 (1.8)
Laryngitis	0	1 (0.9)	3 (2.8)	4 (1.5)
Rhinitis	0	2 (1.8)	1 (0.9)	4 (1.5)
Sinusitis	1 (0.9)	2 (1.8)	2 (1.9)	4 (1.5)
Viral infection	1 (0.9)	3 (2.7)	1 (0.9)	4 (1.5)
Respiratory tract infection	0	1 (0.9)	2 (1.9)	3 (1.1)
Tonsillitis	1 (0.9)	2 (1.8)	0	2 (0.7)
Oral infection	0	0	2 (1.9)	2 (0.7)
Vulvovaginal mycotic infection	1 (0.9)	2 (1.8)	0	2 (0.7)

CZP=certolizumab; PBO=placebo; AE=adverse event; SOC=system organ class
†=entire placebo group, CZP data from placebo subjects were not utilized; ‡=includes CZP 200mg, CZP 400mg, and the escaped placebo subjects with their CZP data
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 11-10, page 237-8

Malignancies

There were no malignancies reported during the 24 week double-blind treatment period.

Hepatotoxicity

TNF-inhibitors have been associated with elevated liver enzymes and hepatitis. Potential hepatotoxicity or elevated liver enzymes are mentioned as an adverse reaction in all of the approved TNF-inhibitor labels. Therefore, it is important to assess for certolizumab-associated hepatotoxicity.

Table 41 displays the proportion of patients with abnormal post-baseline aspartate aminotransferase (AST) and alanine aminotransferase (ALT) measurements in trial AS001 through Week 24. Table 41 is stratified by whether AST and ALT values were normal or abnormal at baseline. Patients were excluded from the trial if their baseline liver function tests exceeded 2x upper limit of normal (ULN); therefore, it was possible for patients to have abnormal liver enzymes and enroll in the trial.

Almost all patients enrolled had normal AST and ALT levels at baseline. Of the patients with normal AST at baseline, a similar proportion of patients had AST elevations post-baseline in the certolizumab and placebo groups. Of the patients with normal ALT at baseline, a higher proportion of patients treated with certolizumab had ALT elevations of 1-2 x ULN post-baseline than patients on placebo. For patients with baseline elevations in AST or ALT, a slightly higher proportion of patients in the certolizumab group compared with the placebo group had post-baseline AST or ALT elevations. However, the majority of these elevations were minimal as only one patient treated with certolizumab had an AST value ≥3 x ULN post-baseline.

Table 42 displays elevations of liver functions tests greater than 3x ULN. The proportion of patients experiencing these liver function tests abnormalities were greater with certolizumab than placebo, however the overall frequency of liver function tests greater than 3x ULN was low. No patients experienced bilirubin levels above the ULN with an ALT or AST greater than 3x ULN. Thus, there were no cases of liver function test abnormalities that were suggestive of drug-induced liver injury.

Table 41: Post-baseline ALT and AST measurements during the 24-week double blind treatment period in trial AS001 stratified by whether baseline AST and ALT values were normal or elevated (Safety Set)

Preferred term	Placebo† n (%)	All CZP‡ n (%)
N	107	274
Patients with baseline <ULN		
AST		
Patients with baseline <ULN	105 (98.1)	269 (98.2)
Maximum post-baseline value§		
1-<2x ULN	7 (6.7)	23 (8.6)
2-<3x ULN	2 (1.9)	5 (1.9)
≥3x ULN	0	2 (0.7)
ALT		
Patients with baseline <ULN	105 (98.1)	266 (97.1)
Maximum post-baseline value§		
1-<2x ULN	8 (7.6)	45 (16.9)
2-<3x ULN	2 (1.9)	8 (3.0)
≥3x ULN	1 (1.0)	3 (1.1)
Patients with baseline >ULN		
AST		
Patients with baseline >ULN	2 (1.9)	5 (1.8)
Maximum post-baseline value‖		
1-<2x ULN	0	3 (60)
2-<3x ULN	0	0
≥3x ULN	0	1 (20)
ALT		
Patients with baseline >ULN	2 (1.9)	8 (2.9)
Maximum post-baseline value‖		
1-<2x ULN	1 (50)	4 (50)
2-<3x ULN	0	3 (37.5)
≥3x ULN	0	0

CZP=certolizumab; PBO=placebo; AE=adverse event
†=entire placebo group, CZP data from placebo subjects were not utilized; ‡=includes CZP 200mg, CZP 400mg, and the escaped placebo subjects with their CZP data; §=this event was reported at the subject's Early Termination Visit
§=Denominator for percentage calculation is the number of patients with a baseline AST/ALT <ULN
‖=Denominator for percentage calculation is the number of patients with a baseline AST/ALT >ULN
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 11-12, page 241

Table 42: Post-baseline elevations in liver function tests greater than 3x upper limit of normal during the 24-week double blind treatment period (Safety Set)

Preferred term	Placebo† n (%)	CZP 200mg Q2W n (%)	CZP 400mg Q4W n (%)	All CZP‡ n (%)
N	107	111	107	274
AST				
≥3x ULN	0	3 (2.7)	0	3 (1.1)
≥5x ULN	0	2 (1.8)	0	2 (0.7)
≥10x ULN	0	0	0	0
≥20x ULN	0	0	0	0
ALT				
≥3x ULN	1 (0.9)	2 (1.8)	1 (0.9)	3 (1.1)
≥5x ULN	0	1 (0.9)	0	1 (0.4)
≥10x ULN	0	1 (0.9)	0	1 (0.4)
≥20x ULN	0	0	0	0
AST or ALT				
≥3x ULN	1 (0.9)	4 (3.6)	1 (0.9)	5 (1.8)
≥5x ULN	0	2 (1.8)	0	2 (0.7)
≥10x ULN	0	1 (0.9)	0	1 (0.4)
≥20x ULN	0	0	0	0
Bilirubin				
≥1.5x ULN	0	2 (1.8)	0	2 (0.7)
Bilirubin ≥1x ULN and ALT or AST ≥3x ULN	0	0	0	0

CZP=certolizumab; PBO=placebo; AE=adverse event
†=entire placebo group, CZP data from placebo subjects were not utilized; ‡=includes CZP 200mg, CZP 400mg, and the escaped placebo subjects with their CZP data; §=this event was reported at the subject's Early Termination Visit
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 11-13, page 242

There were four SAEs or adverse events leading to discontinuation related to a hepatic event or liver function test elevation. One of the AEs occurred in a patient receiving placebo, rather than certolizumab. None of the remaining three AEs appeared to be secondary to certolizumab exposure as there were other confounding factors.

Cardiovascular Events
All five approved TNF-inhibitors have warnings and precautions regarding the risk of congestive heart failure (CHF).

In trial AS001, patients with a history of CHF, including medically controlled, asymptomatic CHF were appropriately excluded from participation. In the 24-week double-blind period of trial AS001, there were no adverse events related to CHF.

The proportion of patients with adverse events in the cardiac disorders system organ class was twice as high in the certolizumab group compared with the placebo group (Table 43). However, the number of patients with events was small (5 in the certolizumab group compared with 1 in the placebo group). Further, the differences were not attributed to any single preferred term and no preferred term had more than one patient with an event. The proportion of patients with adverse events in the

vascular disorders system organ class appeared balanced between the certolizumab and placebo groups (Table 43).

Table 43: Adverse events in the cardiac and vascular system organ class during the 24-week double blind treatment period (Safety Set)

Preferred term	Placebo† n (%)	CZP 200mg Q2W n (%)	CZP 400mg Q4W n (%)	All CZP‡ n (%)
N	107	111	107	274
Any AE in the Cardiac disorders SOC	1 (0.9)	2 (1.8)	2 (1.9)	5 (1.8)
Tachycardia	0	1 (0.9)	0	2 (0.7)
Supraventricular extrasystoles	0	0	1 (0.9)	1 (0.4)
Supraventricular tachycardia	0	0	1 (0.9)	1 (0.4)
Ventricular extrasystoles	0	1 (0.9)	0	1 (0.4)
Sinus tachycardia	1 (0.9)	0	0	0
Any AE in the Vascular disorders SOC	6 (5.6)	4 (3.6)	5 (4.7)	14 (5.1)
Hypertension	4 (3.7)	3 (2.7)	2 (1.9)	8 (2.9)
Hypotension	1 (0.9)	0	2 (1.9)	2 (0.7)
Aortic aneurysm	0	0	0	1 (0.4)
Hematoma	0	0	1 (0.9)	1 (0.4)
Hot flush	0	1 (0.9)	0	1 (0.4)
Subclavian artery stenosis	0	0	0	1 (0.4)
Circulatory collapse	1 (0.9)	0	0	0

CZP=certolizumab; PBO=placebo; AE=adverse event
†=entire placebo group, CZP data from placebo subjects were not utilized; ‡=includes CZP 200mg, CZP 400mg, and the escaped placebo subjects with their CZP data; §=this event was reported at the subject's Early Termination Visit
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 11-11, page 239

Demyelinating Disorders
There were no adverse events of demyelinating disorders or notable neurological serious adverse events during the 24-week double-blind treatment period.

Injection Site Reactions
Injection site reactions were more common in the all certolizumab group (6.6%) compared with the placebo group (0.9%). The proportion of patients with injection site reactions was higher in patients receiving certolizumab 200mg Q2W (9.0%) compared with certolizumab 400mg Q4W (4.7%). The increased frequency of injection site reactions is most likely related to more frequent administration of certolizumab.

Autoimmune Disorders
One patient developed pustular psoriasis during the 24-week double blind treatment period. There were no other autoimmune disorders during the 24-week double blind treatment period.

Hematologic Cytopenias
All five approved TNF-inhibitors have warnings regarding hematologic cytopenias including pancytopenia, aplastic anemia, leukopenia, and thrombocytopenia. Thus, it is important to asses for these cytopenias in the certolizumab safety database.

In the 24-week double-blind period of trial AS001, reports of cytopenias were rare and seemed balanced between the certolizumab and placebo groups. Specific cytopenias that occurred during the trial were anemia (1.1% in the certolizumab group and 3.7% in placebo group), leukopenia (1.1% in the certolizumab group and 0% in the placebo group), and neutropenia (1.1% in the certolizumab group and 0% in the placebo group).

Markedly abnormal hematology values were defined as laboratory values grade 3 or 4 according to the Rheumatology Common Toxicity Criteria version 3.0 (RCTC v.3.0). No patients had markedly abnormal hematology values for the following parameters: erythrocytes, platelets, and leukocytes (Table 44). The frequency of markedly abnormal hemoglobin and neutrophil parameters were similar in the placebo and certolizumab groups. The frequency of markedly abnormal lymphocytes was higher in the placebo (11.2%) than the certolizumab group (2.9%). Thus, certolizumab did not appear to be associated with marked laboratory abnormalities.

Table 44: Adverse events in the blood and lymphatic system organ class with preferred terms related to cytopenias (Safety Set)

Preferred term	Placebo† N (%)	CZP 200mg Q2W n (%)	CZP 400mg Q4W n (%)	All CZP‡ n (%)
N	107	111	107	274
Blood and lymphatic system disorders	5 (4.7)	5 (4.5)	5 (4.7)	10 (3.6)
Iron deficiency anemia	1 (0.9)	0	0	0
Anemia	4 (3.7)	1 (0.9)	2 (1.9)	3 (1.1)
Leukopenia	0	0	2 (1.9)	3 (1.1)
Neutropenia	0	2 (1.8)	1 (0.9)	3 (1.1)

CZP=certolizumab; PBO=placebo; AE=adverse event
†=entire placebo group, CZP data from placebo subjects were not utilized; ‡=includes CZP 200mg, CZP 400mg, and the escaped placebo subjects with their CZP data
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 8.4.1, pages 3098-9

Table 45: Patients with at least one markedly abnormal post-baseline cytopenias in the 24 week double blind trial (Safety Set)

Preferred term	Placebo† N (%)	CZP 200mg Q2W n (%)	CZP 400mg Q4W n (%)	All CZP‡ n (%)
N	107	111	107	274
Any Marked Abnormality				
Erythrocytes	0	0	0	0
Hemoglobin	4 (3.7)	1 (0.9)	0	1 (0.4)
Platelet	0	0	0	0
Leukocytes	0	0	0	0
Neutrophils	0	1 (0.9)	0	2 (0.7)
Lymphocytes	12 (11.2)	2 (1.8)	4 (3.7)	8 (2.9)

CZP=certolizumab; PBO=placebo; AE=adverse event
†=entire placebo group, CZP data from placebo subjects were not utilized; ‡=includes CZP 200mg, CZP 400mg, and the escaped placebo subjects with their CZP data
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 9.7.1, pages 5849-60

Other
Two other adverse events of interest were alopecia and retinal vein occlusion. Two subjects reported alopecia in the all certolizumab group during the 24-week double-blind treatment period (0.7%). Both events were non-serious and mild in intensity. Alopecia is currently listed in the adverse events section of the certolizumab label and the postmarketing experience section of the adalimumab label. Thus, alopecia does not represent a new safety concern with TNF-inhibitors.

One SAE of retinal vein occlusion occurred during trial AS001. The patient experienced loss of vision in the left eye. A slit lamp examination was consistent with central vein occlusion. Certolizumab treatment was interrupted. The retinal vein occlusion resolved 20 days after onset at which time certolizumab was restarted and the patient completed the trial. None of the currently approved TNF-inhibitors mention retinal vein occlusion in their labels. Thrombosis is mentioned in one TNF-inhibitor label. A previous population-based trial in which retinal vein occlusions were detected at baseline and at a 5-year follow-up examination[11] found that retinal vein occlusion is infrequent in the population with a prevalence of central retinal vein occlusion of 0.1%. Thus, retinal vein occlusion is an uncommon event. However, there are no additional data to suggest that this is a unique safety concern in patients with axial SpA.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 46 displays the common AEs in trial AS001 of certolizumab in axial SpA through Week 24. A slightly higher proportion of patients in the certolizumab group compared to the placebo group had AEs. The largest difference in the proportion of AEs for patients treated with certolizumab compared to placebo were noted for blood creatine phosphokinase increased (5% vs. 2%), injection site erythema (3% vs. 0%), rash (4% vs. 2%), and folliculitis (2% vs. 0%).

The most common AEs in the AS subpopulation were similar to the overall population.

Table 46: Adverse events (with frequency at least 2% in the all certolizumab group) in Trial AS001 in overall axial SpA population (Safety Set)

System organ class Preferred term	Placebo† n (%)	CZP 200mg Q2W n (%)	CZP 400mg Q4W n (%)	All CZP‡ n (%)
N	107	111	107	274
Any adverse event	67 (62.6)	85 (76.6)	80 (74.8)	193 (70.4)
Gastrointestinal disorder	15 (14.0)	15 (13.5)	15 (14.0)	38 (13.9)
Nausea	1 (0.9)	4 (3.6)	2 (1.9)	7 (2.6)
General disorders and administration site conditions	8 (7.5)	17 (15.3)	11 (10.3)	34 (12.4)
Fatigue	1 (0.9)	3 (2.7)	3 (2.8)	6 (2.2)
Injection site erythema	0	3 (2.7)	3 (2.8)	7 (2.6)
Infections and infestations	25 (23.4)	43 (38.7)	41 (38.3)	95 (34.7)
Folliculitis	0	3 (2.7)	2 (1.9)	6 (2.2)
Bronchitis	1 (0.9)	4 (3.6)	1 (0.9)	6 (2.2)
Nasopharyngitis	7 (6.5)	11 (9.9)	11 (10.3)	24 (8.8)
Upper respiratory tract infection	3 (2.8)	6 (5.4)	4 (3.7)	11 (4.0)
Pharyngitis	1 (0.9)	5 (4.5)	1 (0.9)	7 (2.6)
Urinary tract infection	4 (3.7)	2 (1.8)	3 (2.8)	7 (2.6)
Investigations	7 (6.5)	19 (17.1)	16 (15.0)	37 (13.5)
Blood creatine phosphokinase increased	2 (1.9)	7 (6.3)	6 (5.6)	14 (5.1)
Nervous system disorders	12 (11.2)	12 (10.8)	14 (13.1)	28 (10.2)
Headache	7 (6.5)	7 (6.3)	9 (8.4)	17 (6.2)
Respiratory, thoracic, and mediastinal disorders	6 (5.6)	14 (2.6)	5 (4.7)	19 (6.9)
Cough	1 (0.9)	5 (4.5)	2 (1.9)	7 (2.6)
Skin and subcutaneous tissue disorder	14 (13.1)	17 (15.3)	16 (15.0)	40 (14.6)
Rash	2 (1.9)	3 (2.7)	4 (3.7)	12 (4.4)
Vascular disorder	6 (5.6)	4 (3.6)	5 (4.7)	14 (5.1)
Hypertension	4 (3.7)	3 (2.7)	2 (1.9)	8 (2.9)

Axial SpA=axial spondyloarthritis; CZP=certolizumab; PBO=placebo; AE=adverse event
†=entire placebo group, CZP data from placebo subjects were not utilized; ‡=includes CZP 200mg, CZP 400mg, and the escaped placebo subjects with their CZP data
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 11-3, pages 227-8

7.4.2 Laboratory Findings

See Section 7.3.5 for a discussion of post-baseline elevation of liver enzymes and cytopenias in trial AS001.

TNF-inhibitors are not known to be associated with electrolyte abnormalities. In trial AS001, markedly abnormal laboratory values were defined as laboratory values grade 3 or 4. Markedly abnormal biochemistry values were not reported in the overall axial spondyloarthritis population for the following parameters: sodium, potassium, calcium, creatinine, urate, alkaline phosphatase, and bilirubin. Markedly abnormal biochemistry values were reported for both the placebo and all certolizumab groups in creatinine kinase (3.7% vs. 4.4%, respectively), glucose (1.9% vs. 1.5%), and ALT (0.9% vs. 1.1%). Markedly abnormal AST values were reported only in the all certolizumab group

(1.1%). Thus, in general, the certolizumab and placebo groups had similar proportions of markedly abnormal biochemistry values.

In general, shifts in biochemistry laboratory values from baseline to the last post-baseline value were similar in the placebo and all certolizumab groups. A slightly higher percentage of patients treated with certolizumab than placebo had elevations in creatine phosphokinase (7.5% vs. 9.9%, respectively). These elevations were not associated with clinical events. Thus, there is no clear evidence that certolizumab is associated with electrolyte abnormalities.

7.4.3 Vital Signs

Vital signs were monitored at all clinic visits. Based on mean and median changes from baseline, no clinically important changes in systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate or body temperature were noted.

Hypertension was defined as either a systolic blood pressure ≥140 or diastolic blood pressure ≥90 at 2 or more consecutive visits. The proportion of patients with hypertension was similar between the all certolizumab and placebo groups (16.8%. vs. 17.8%, respectively).

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed in trial AS001. This is reasonable as TNF-inhibitors are not known to be associated with the development of ECG abnormalities.

There was one serious cardiac events related to an arrhythmia in trial AS001. The patient was a 20 year old man receiving certolizumab 400mg Q4W who developed supraventricular tachycardia 127 days after initiating trial drug. Of note, “arrhythmia” was listed in his past medical history. The event required hospitalization and medical management. The event resolved two days later. The trial drug was restarted 14 days after the event. No other serious adverse events related to cardiac disorders were noted during the 24-week trial. Thus, there is no clear evidence of an association of certolizumab with concerning arrhythmias in trial AS001.

7.4.5 Special Safety Studies/Clinical Trials

This supplement did not involve special safety studies or clinical trials.

7.4.6 Immunogenicity

Table 47 displays the number and proportion of patients who received certolizumab in trial AS001 who developed anti-certolizumab antibodies. The proportion of certolizumab-treated patients who developed anti-certolizumab antibodies was low.

There did not appear to be a relationship between the development of anti-certolizumab antibodies and the occurrence of adverse events.

Table 47: Incidence of adverse events by anti-certolizumab antibody status for patients with certolizumab exposure (Safety Set)

	Anti-CZP status			
	Any n (%)	Negative n (%)	Positive n (%)	After the onset of positive antibody status n (%)
N	274	246	10	10
Any adverse events	193 (70.4)	172 (69.9)	7 (70.0)	4 (40.0)
Serious adverse event	13 (4.7)	11 (4.5)	0	0
Discontinuation due to adverse event	6 (2.2)	6 (2.4)	0	0
Death	0	0	0	0

CZP=certolizumab
Source: Adapted from Study Report Body (Module 5.3.5.1.3), submitted 12/14/12, table 8.14.1, page 4139

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In general, the occurrence of adverse events was fairly balanced for the certolizumab 200mg Q2W and 400mg Q4W groups. The percentage of patients with AEs leading to discontinuation and SAEs was slightly higher in the certolizumab 400mg Q4W group than the certolizumab 200mg Q2W group. In contrast, the percentage of patients with common AEs was slightly higher in the certolizumab 200mg Q2W group than the 400mg Q4W group. There was no clear relationship between the different doses of certolizumab in terms of their safety profiles.

7.5.2 Time Dependency for Adverse Events

The Sponsor did not perform a specific analysis of safety data for time dependency of adverse events. Given the relatively short length of the trial (24 weeks) and the low discontinuation rate (8.3% overall), it is reasonable to evaluate the data based on percentages of adverse events rather than adjusting for patients years of exposure.

7.5.3 Drug-Demographic Interactions

The Sponsor performed subgroup safety analyses based on gender. In the all certolizumab group, females had a higher proportion of adverse events compared to males (89.1% vs. 77.6%, respectively). There were no differences between males and females with regard to reporting of severe AEs, SAEs, or AEs leading to discontinuation. As seen in the overall population, the percentage of AEs was higher in the certolizumab 200mg Q2W group compared with the certolizumab 400mg Q4W group in both males (82.6% vs. 73.1%) and females (93.9% vs. 83.0%).

7.5.4 Drug-Disease Interactions

Subgroup analyses based on central interpretation of screening radiographs demonstrated no notable differences in the safety profile compared to the overall population studied.

7.5.5 Drug-Drug Interactions

No new drug-drug interaction data were submitted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No specific trials were conducted to assess for carcinogenicity in humans.

7.6.2 Human Reproduction and Pregnancy Data

No studies of certolizumab were conducted in pregnant or lactating women. There were no pregnancies during the double-blind treatment period of study AS001. However, three pregnancies occurred in study AS001 during the clinical cut period. Minimal information is available regarding these pregnancies. One pregnancy was associated with intra-uterine death, one pregnancy was ongoing, and one pregnancy (in which the male was exposed to certolizumab) was associated with intra-uterine death. Additional details regarding these pregnancies are provided in Table 48. Given the limited information available, definitive conclusions are not possible regarding any relationship between certolizumab and pregnancy outcomes.

Table 48: Outcomes of 3 pregnancies in patients who received certolizumab during study AS001

Treatment	Patient	Outcome
Female		
Not applicable (1 year and 3 months after exposure to investigational agent)	ID not provided	Retrospective pregnancy report; patient underwent a therapeutic abortion
CZP 200mg Q2W	(b) (6)	Patient became pregnant while receiving CZP; pregnancy was ongoing at the time of the report; outcome not provided
Male		
CZP 400mg Q4W	(b) (6)	Intra-uterine death diagnosed at 11th week of pregnancy

CZP=certolizumab pegol
Source: FDA generated

The Sponsor submitted a cumulative postmarketing surveillance report covering September 7, 2007 (International Birth Date) to May 31, 2012 (data lock point). For the purposes of the report, only cases classified as serious (with or without fatal outcomes)

were described. The report types were spontaneously reported cases including non-interventional studies. The report did not include cases related to interventional clinical trial cases and non-serious cases. In this report, 48 cases were identified with an event described in the SOC Pregnancy, puerperium and perinatal conditions. These 48 cases included 40 females and 8 males. The Sponsor reported additional clinical details of some of these cases. The most frequent underlying disease indication was Crohn's disease and the most frequent outcome was spontaneous abortion. Limited clinical details were available and there was no clear relationship between the use of certolizumab and the pregnancy outcome. The current certolizumab label should be used during pregnancy only if clearly needed.

7.6.3 Pediatrics and Assessment of Effects on Growth

The juvenile equivalents of AS are extremely rare. The Sponsor submitted a full waiver request for pediatric patients under the age of 18 years with axial SpA. The Sponsor's justification is based on the argument that studies would be impossible or impractical due to the uncommon occurrence of axial SpA and inflammatory back pain in children. The Agency has previously waived studies for juvenile equivalents of AS based on similar rationale.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No information was provided regarding potential overdose, drug abuse potential, withdrawal and rebound.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 120 day safety update. Data from this submission did not reveal any new issues not already commented on.

8 Postmarket Experience

The Sponsor submitted a postmarketing surveillance report for certolizumab for the reporting period of September 7, 2007 through May 31, 2012 to summarize the postmarketing experience. For the purpose of the report, only cases classified as serious (with or without fatal outcome) were described. The included reports were submitted spontaneously. While there are limitations in the interpretation of postmarketing, spontaneous reports, no new safety information was included in the submission that changed the known risks of certolizumab.

9 Appendices

9.1 Literature Review/References

Reference List

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11. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. Trans Am Ophthalmol Soc 2000;98:133-141.

9.2 Labeling Recommendations

The following are major changes recommended for the sponsor's proposed labeling for certolizumab. These recommendations may change after internal labeling discussions and after labeling discussions with the sponsor.

Indications and Usage

1. The sponsor proposed the following indicatio (b) (4) (b) (4) (b) (4) As the majority of the patients enrolled in trial AS001 had AS and there are insufficient data available to support the broader indication or the indication of non-radiographic axial spondyloarthritis, the indication statement should only refer to ankylosing spondylitis.

Warnings and Precautions

2. The sponsor proposed updatin (b) (4) (b) (4) (b) (4) the division disagreed with inclusion of the propose (b) (4) in the label.

3. The sponsor proposed additional language regarding postmarketing cases of hepatosplenic T-cell lymphoma. This section was discussed with the Division of Gastroenterology and Inborn Errors Products (DGIEP) and additional language was recommended regarding this potential risk.

Adverse Reactions

4. Similar to in Warnings and Precautions, the Sponsor recommended labeling changes tha (b) (4) As previously noted, the division disagreed with inclusion of the proposed (b) (4) (b) (4)

Clinical Studies

5. The description of study AS001 was modified to emphasize that the majority of patients in the study had AS and a limited number of patients had other types of axial spondyloarthritis.
6. Data relating to (b) (4) (b) (4) inclusion in the label were removed (b) (4) (b) (4) (b) (4) (b) (4) were removed from the label.

Medication Guide
8. Multiple changes to the medication guide are recommended as part of an ongoing supplement review (125160/213, certolizumab for psoriatic arthritis). These recommended changes maintain consistency with the approved Medication Guide for other recently approved TNF inhibitors.

9.3 Advisory Committee Meeting

On July 22, 2013, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) discussed the implications of the ASAS classification criteria for axial SpA in terms of drug development and approval by the FDA. This was a general topic discussion, utilizing publically available scientific information. Data from the pending sBLA were not reviewed. In general, the Arthritis Advisory Committee (AAC) members felt that there are limitations in terms of the available epidemiological data on axial SpA, but that this does not preclude studying patients with axial SpA. In general, the committee members felt they would consider approving products for axial SpA if the data were adequate.

On July 23, 2013, DPARP and the Sponsor discussed the findings from the certolizumab sBLA at an Arthritis Advisory Committee meeting. The Sponsor's presentation focused on the efficacy results in the overall study population in trial AS001. In addition, the Sponsor discussed that findings were generally consistent in patients with AS and nr-axSpA, regardless of the method of classification. The Sponsor noted that not all patients had MRIs during the study, thus it is unclear exactly how many patients met the ASAS imaging criteria for axial SpA. FDA's presentation focused on the limited number of patients without imaging evidence of sacroiliitis. The committee members were divided on whether the data provided substantial evidence that certolizumab provides a clinically meaningful beneficial effect in the treatment of active axial spondyloarthritis, including patients with ankylosing spondylitis (8 yes, 5 no, 1 abstain). The committee members commented that the definition of "active" axial spondyloarthritis was unclear and it was uncertain whether the small number of patients exposed is sufficient enough to support a new indication. The majority of the committee members felt that safety profile was adequate to support approval of certolizumab for active axial SpA (13 yes, 1 no, 1 abstain) due to lack of new safety signals identified in axial SpA. Members did express concerns regarding serious infection and CK elevations. Regarding the overall approval question, the committee was divided

regarding whether there were adequate safety and efficacy data to support approval of certolizumab for the treatment of active axial SpA (7 yes, 6 no, 1 abstain). During discussion of the questions, multiple panel members expressed concerns regarding the ability to characterize patients into the subgroups of AS and nr-axSpA due to limitations in x-ray classification. Further some members noted that the number of patients studied was small and they wanted more data and clarity on the definition of active axial SpA.

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/s/

JANET W MAYNARD
09/12/2013

SARAH K YIM
09/12/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Origs237

OTHER REVIEW(S)

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2019015
IND/NDA/BLA Number/Referenced IND for NDA/BLA:	BLA 125160
Sponsor/Applicant:	UCB, Inc.
Established Name/Trade Name:	CIMZIA (certolizumab pegol (CZP))
Indication:	non-radiographic axial spondyloarthritis (nr-axSpA)
Meeting Type/Deliverable:	
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Clinical Reviewer/Team Leader (TL)	Suzette Peng
Review Division Project Manager:	Nina Ton
COA Reviewer:	Wen-Hung Chen
COA TL:	
COA Associate Director:	Elektra Papadopoulos
Date Consult Request Received:	January 9, 2019
Date COA Review Completed:	March 25, 2019

Please check all that apply: ☐Rare Disease/Orphan Designation
☐Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to BLA 125160 for certolizumab pegol injection, for subcutaneous use. The sponsor is in phase 3 of their drug development program, with a completed and an on-going phase 3 clinical trials to support marketing approval. The proposed indication is treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation.

The applicant used the following patient-reported outcome (PRO) assessment in their completed multicenter, randomized, double-blind, parallel-group, placebo controlled clinical study, AS001, to evaluate the efficacy and safety of certolizumab pegol (CZP) (200mg Q2W or 400mg Q4W) in adult subjects with active axSpA, and included both AS and nr-axSpA subjects.

Reference ID: 4409249

The review concludes that the evidence submitted by the applicant is sufficient to demonstrate that the ASQoL is fit-for-purpose[3] for this development program to measure concepts relevant and important to the patients with active nr-axSpA in the context of use (see Table 2). If the Division determines that ASQoL can be included in the labeling, we recommend using the following language is more accurately reflecting the concept assessed by that ASQoL:

"In Study nr-axSpA-01, patients treated with CIMZIA achieved greater improvement in disease related impacts at Week 12 from baseline compared to placebo-treated patients as assessed by Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL)."

While the ASQoL appears fit-for-purpose for this development program, we have noted the following limitations as part of our review.

- The ASQoL is that it features binary response options, which may not be sufficiently granular to detect small but meaningful treatment effects. This also may be an impediment to interpretation because it forces patients to choose among extremes that may not necessarily reflect their status.
- The ASQoL instructs patients to consider how much each symptom or impact affects them "currently". This instruction is likely to be interpreted differently by different respondents and make the results more difficult to interpret. For example, one item, "the pain is always there," requires the respondent to think over an unspecified period in the

[1] Please see Section B 1.3 of this COA review for the complete endpoint hierarchy.
[2] The ASQoL has been included in the labeling of golimumab (SIMPONI ARIA) for the treatment of ankylosing spondylitis (AS)
[3] Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; https://www.ncbi.nlm.nih.gov/books/NBK338448/)

past, which could vary markedly from one patient to another. The term "always" implies over a period, which is incongruent with the instructions which state "currently".
- The emotional domain may also be difficult to link to the effect of a drug. For example, one item (Sometimes I feel like crying) is somewhat vague and may function differently among different demographic groups. For this as well as other multi-item COAs, we recommend evaluating treatment effect at the item or domain level to evaluate whether the components of the instrument are contributing similarly to the overall treatment effect, and if not, we note this and communicate it appropriately.

Given these limitations, we recommend that future sponsors discuss with the Agency the best PRO measurement strategy for their product early in drug development.

B. BACKGROUND

AxSpA, spondyloarthritis with predominantly axial involvement, is a chronic inflammatory rheumatic disease. AxSpA comprises the disease subgroup ankylosing spondylitis (AS), as well as a disease subgroup characterized by little or no changes on plain radiographs, referred to as non-radiographic axial spondyloarthritis (nr-axSpA).

Certolizumab pegol (CZP) is a humanized fragment antigen binding prime (Fab') conjugated to polyethylene glycol (PEG) with specificity for human TNFα. Certolizumab pegol has demonstrated efficacy in clinical studies of Crohn's disease (CD), psoriasis, psoriatic arthritis, and RA. In this study, the efficacy of CZP was evaluated in subjects with axSpA who met the new Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA, including subjects with AS also meeting the modified New York (mNY) definitive classification criteria. The objective of this study was to demonstrate the effects of CZP in the treatment of axSpA. Two dose regimens of CZP were selected for this study, reflecting 2 different frequencies of administration: 3 loading doses of CZP 400mg administered subcutaneously (sc) at Weeks 0, 2, and 4 followed by either CZP 200mg every 2 weeks (Q2W) or CZP 400mg every 4 weeks (Q4W).

The applicant is seeking the inclusion of ASQoL score to achieve the first ever FDA labelling claim within the nr-axSpA population by demonstrating that it is a psychometrically reliable, valid, and treatment-responsive endpoint.

Materials reviewed:

- Ankylosing Spondylitis Quality of Life Questionnaire Evidence Dossier, Final Version; September 4, 2018; UCB.
- Clinical Overview, Certolizumab pegol; September 27, 2018; UCB.
- Summary of Clinical Efficacy, Certolizumab pegol; September 26, 2018; UCB.
- Final Clinical Study Report, Study AS001, Certolizumab pegol; July 18, 2016, UCB
- FDA BLA 125433 golimumab AS PsA CDTL review FINAL; October 20, 2017 (Reference ID #4169819)

Reference ID: 4409249

B. CLINICAL OUTCOME ASSESSMENT REVIEW

1 FIT-FOR-PURPOSE SUMMARY

Table 2. Fit-for-purpose assessment (based on available evidence)

COA Name(s)	Attribute sufficiently established[4]	Supported by:	Location of Supporting Materials
Ankylosing Spondylitis Quality of Life (ASQoL)	☒ Yes ☐ Potentially - insufficient evidence available; additional information is needed ☐ No	☒ Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment) ☒ Evidence of content validity ☒ Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) ☒ COA well-defined and concept is able to be accurately communicated ☒ COA is able to detect change ☐ COA is culturally adapted and adequately translated, if appropriate	ASQoL Evidence Dossier Final (04 September 2018)

2 CONTEXT OF USE

2.1 Clinical Trial Population

The target population for Study AS001 are adults with active nr-axSpA who have had an inadequate response to, have a contraindication to, or are intolerant to ≥2 NSAIDs. Subjects must have had a documented diagnosis of adult onset axSpA and met the ASAS classification criteria for axSpA, had back pain of at least 12 months' duration, and had active disease defined by a BASDAI score ≥4, and spinal pain ≥4 on a 0 to 10 NRS.

A complete list of the inclusion and exclusion criteria is summarized in Clinical Overview for certolizumab pegol, dated September 27, 2018.

2.2 Clinical Trial Design

Table 3 describes the clinical trial design of Study AS001.

[4] See Sections 5 and 6 of this COA review for more detailed information.

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Table 3. Clinical Trial Design for Study AS001

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	☐ Single arm ☐ Open label ☒ Double-blind ☒ Randomized ☒ Placebo-/Vehicle-controlled ☐ Active comparator-controlled ☐ Cross-over ☒ Multinational ☐ Non-inferiority	The trial contained 5 study periods: Screening: Weeks -1 to -5 weeks; Double blind 1, placebo-control: Weeks 0 to 24; Double blind 2, no placebo control: Weeks 24 to 48; Period 4, open-label: Weeks 48 to 204; Period 4: safety follow-up	Yes

Refer to the Final Clinical Study Report, Study AS001, Certolizumab pegol (dated July 18, 2016) for more details on the clinical trial design.

2.3 Endpoint Position, Definition, and Assessment Schedule

Table 4 describes the placement of the COA in the endpoint hierarchy, including the endpoint definition and assessment schedule for Study AS001.

Table 4. Endpoint Position, Definition, and Assessment Schedule for Study AS001

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Primary (COA and/or biomarker)	Assessment of SpondyloArthritis international Society 20% response criteria (ASAS20)	• Patient global assessment of disease activity • Pain assessment (the total spinal pain NRS score) • Function (represented by BASFI) • Inflammation (the mean of the BASDAI Questions 5 and 6)	ASAS20 response at Week 12. (The ASAS20 response is defined as an improvement of at least 20% and absolute improvement of at least 1 unit on a 0 to 10 NRS in at least 3 of the 4 domains)	☐ Daily ☐ Weekly ☐ Monthly ☒ Other: ☐ Assessment at cross-over or early discontinuation

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Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Secondary	ASAS20	Same as the primary endpoint	ASAS20 response at Week 24	☐ Daily ☐ Weekly ☐ Monthly ☒ Other: ☐ Assessment at cross-over or early discontinuation
Secondary ☒ Multiplicity adjusted	Bath Ankylosing Spondylitis Functional Index (BASFI)	Function impairment	Change from Baseline in BASFI to Weeks 12 and 24	☐ Daily ☐ Weekly ☐ Monthly ☒ Other: ☐ Assessment at cross-over or early discontinuation
Secondary ☒ Multiplicity adjusted	Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	Disease activity	Change from Baseline in BASDAI to Weeks 12 and 24	☐ Daily ☐ Weekly ☐ Monthly ☒ Other: ☐ Assessment at cross-over or early discontinuation
Secondary ☒ Multiplicity adjusted	Bath Ankylosing Spondylitis Metrology Index (BASMI) linear	Spinal mobility	Change from Baseline in BASMI linear to Weeks 12 and 24	☐ Daily ☐ Weekly ☐ Monthly ☒ Other: ☐ Assessment at cross-over or early discontinuation
Secondary ☒ Multiplicity adjusted	ASspiMRI-a in the Berlin modification	MRI for inflammatory activity	Change from Baseline in spine ASspiMRI-a in the Berlin modification (MRI parameter) to Week 12	☐ Daily ☐ Weekly ☐ Monthly ☒ Other: ☐ Assessment at cross-over or early discontinuation

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Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Secondary ☒ Multiplicity adjusted	Sacroiliac (SI) joints Spondyloarthritis Research Consortium of Canada (SPARCC) scores		Change from Baseline in SI joint SPARCC scores (MRI parameter) to Week 12	☒ Daily ☐ Weekly ☐ Monthly ☒ Other: ☐ Assessment at cross-over or early discontinuation
Exploratory ☐ Multiplicity adjusted	ASQoL	Disease related impacts	Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) up to Week 12	☒ Daily ☐ Weekly ☐ Monthly ☒ Other: ☐ Assessment at cross-over or early discontinuation

Reviewer's comment:

The assessment schedule of study endpoints was variable across the duration of the study that began with weekly for Weeks 1 and 2, then extended to bi-weekly or every 4 weeks during the double-blind period 1, and then every 12 weeks or longer thereafter. Refer to the Final Clinical Study Report, Study AS001, Certolizumab pegol (dated July 18, 2016) for more details on the assessment schedule of ASQoL.

2.4 Labeling or promotional claim(s) based on the COA

The sponsor has proposed specific targeted COA-related labeling claims.

The targeted labeling claim is *"In Study nr-axSpA-01, patients treated with CIMZIA achieved* [redacted] (b) (4)

Reviewer's comment:

We recommend using the following language is more accurately reflecting the concept assessed by that ASQoL: *"In Study nr-axSpA-01, patients treated with CIMZIA achieved greater improvement in disease related impacts at Week 12 from baseline compared to placebo-treated patients as assessed by Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL)."*

3 CONCEPTS OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest for the COAs are summarized in Table 5.

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Table 5. Concepts of Interest for COAs Included in Study 5

COA name	Concepts
ASQoL	*Pain, Tiredness, Daily activities, Emotional impacts, Sleep problem*

The conceptual framework for ASQoL are shown in Table 6.

Table 6. Conceptual Framework for ASQoL

Item	Domain (if applicable)	General Concept
9. I have unbearable pain 14. The pain is always there	Pain	Impact of non-radiographic axial-spondyloarthritis
7. I am tired all the time 8. I have to keep stopping what I am doing to rest 12. I get tired easily	Tiredness	
1. My condition limits the places I can go 3. I have difficulty dressing 4. I struggle to do jobs around the house 6. I am unable to join in activities with my family/friends 10. It takes a long time to get going in the morning 11. I am unable to do jobs around the house 16. I find it difficult to wash my hair	Daily Activities	
2. I sometimes feel like crying 13. I often get frustrated 15. I feel I miss out on a lot 17. My condition gets me down 18. I worry about letting people down	Emotional Impacts	
5. It's impossible to sleep	Sleep Problem	

Reviewer's comment:

The qualitative data (i.e., literature review, expert input, and patient interview presented in the ASQoL evidence dossier support that the concepts are relevant and important to the patients and can be interpreted as the impacts related to nr-axSpA.

4 CLINICAL OUTCOME ASSESSMENT

Doward and colleagues developed and validated the ASQoL in 2003 for use in ankylosing spondylitis (AS) as a disease-specific patient-reported quality of life instrument (Doward et al.,

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2003)[5]. ASQoL is comprised of 18 items that include a binary (yes/no) response option. The recall period is as the moment (UK English) or currently (US English). A copy of the ASQoL can be found in Appendix A. The ASQoL score ranges from 0 to 18 with higher score indicating worse disease related impact.

The ASQoL is a self-administered paper-based questionnaire. For the AS001 clinical trial, subjects completed the ASQoL in the clinic. For the AS001 clinical study, the ASQoL was completed at Baseline, Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20 and 24. Subjects who discontinued the study treatment followed an alternate schedule of withdrawal treatment Weeks 0, 12, 24 (and every 12 weeks (Q12W)) until as close as possible to week 52.

5 SCORING ALGORITHM

The original ASQoL as developed by Doward and colleagues is an 18-item ordinal scale that yields a total score ranging from 0-18, with higher scores indicating worse HRQOL. When 1 to 3 responses are missing, a total score can be calculated as T = 18*x/18-m where T is the total score, x is the total score for the items completed and m is the number of missing items (Doward et al., 2003).

The applicant calculated a unit-weighted mean score by averaging the 18 ASQoL items. This mean scoring yielded a proportion score, interpreted as the percent of endorsed items (response of "yes") out of 18; this score ranged from 0 to 1.

Reviewer's comment:

Exploratory factor analysis conducted by the applicant showed that the ASQoL consisted of four domains: (1) activities of daily living (ADLs) and pain, (2) sleep disturbance and activity limitation, (3) emotion, and (4) fatigue. In general, separate scores for each of the domains would be recommended. However, the applicant conducted other psychometric analyses (e.g., IRT, multidimensional IRT, and bi-factor IRT) aimed to demonstrate that a single total score could also be used to summarized adequately the overall disease impacts. Given that the concepts assessed by ASQoL have been deemed relevant and important to the patients, it appears reasonable to use a single total score to reflect the total disease impact.

Note that the developer's scoring stipulates a sum score, however, the applicant used the proportion score based on the rationale that it aids the interpretation purposes and to attenuate the skew in the sum scores. However, only when there is no item-level missing data, mean scores and sum scores are identical in this context.

6 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

[5] Doward, L. C., Spoorenberg, A., Cook, S. A., Whalley, D., Helliwell, P. S., Kay, L. J., Chamberlain, M. A. (2003). Development of the ASQoL: A quality of life instrument specific to ankylosing spondylitis. *Annals of the Rheumatic Diseases*.

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☒ Copy of instrument
☒ Literature review and/or publications
☒ Documentation of expert input
☐ Qualitative study protocols and interview guides for focus group or patient interviews
☒ Chronology of events for item generation, modification, and finalization (item tracking matrix)
☒ Synopsis of qualitative findings
☒ Qualitative summary report with evidence to support item relevance, item stems and response options, and recall period
☒ Quantitative summary report with evidence to support item retention and scoring
☐ Transcripts (if available)

Table 7 documents the adequacy of the content of the COAs.

Table 7. Review of Content Validity for ASQoL

COA Attribute	**Attribute sufficiently established**	**Supported by:**	**Location (i.e. page number) of Supporting Materials**
Face validity	☒ Yes ☐ No	☒ Literature ☒ Clinical input e.g. discussion with clinical reviewer	ASQoL Evidence Dossier Final (04 September 2018)
Content validity	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives ☒ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☒ Target sample for qualitative research is appropriate. ☒ Studied sample for qualitative research adequately represents the target patient population ☒ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☐ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) ☒ COA is culturally adapted and adequately translated ☒ Descriptive statistics (if available)	Section 5 of ASQoL Evidence Dossier Final (04 September 2018)

Reference ID: 4409249

		support content relevance ☐ Other (see Reviewer's comments)	

Reviewer's comment:

A feature of the ASQoL is its dichotomous, Yes/No, item responses. Item responses with only two categories are less common in COAs as it is generally believed that granularity of the disease severity or impact could be better reflected with more response categories (i.e., >2). The drawback of using dichotomous response options is that it may be less sensitive to capture small, but clinically meaningful, change. While, it may seem easier for the patients to select an answer, some patients may be forced to choose a response among two extremes that may not necessarily reflect their conditions.

7 OTHER MEASUREMENT PROPERTIES

To date, the following information has been submitted (check all that apply):

- ☒ Literature review and/or publications
- ☒ Quantitative analysis synopsis
- ☐ Full quantitative analysis plan
- ☒ Quantitative summary report with evidence to support reliability, construct validity, ability to detect change and scoring

Table 8 documents the adequacy of the other measurement properties of the ASQoL.

Table 8. Review of Other Measurement Properties for ASQoL

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Reliability	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ Internal consistency reliability estimates in acceptable range (e.g., Cronbach's $\alpha > 0.70$) ☒ Test-retest reliability (or intra-rater reliability) estimates in acceptable range (e.g., ICC ≥ 0.70) ☐ Inter-rater reliability estimates in acceptable range ☒ Other (see Reviewer's comments)	Section 6.3.3.1 ASQoL Evidence Dossier Final (04 September 2018)
Construct validity	☐ Yes ☒ Potentially – insufficient evidence available; additional information is needed	☒ Relationship to other assessments with similar concepts is as expected ☐ Relationship to other assessments with dissimilar concepts is as expected	Section 6.3.3.2 ASQoL Evidence Dossier Final (04 September 2018)

Reference ID: 4409249

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
	☐ No	☐ COA differentiates between clinically distinct groups (i.e., known groups validity) ☐ COA scores are related to a known gold standard assessment of the same concept ☒ Other (see Reviewer's comments)	
Ability to detect change	☐ Yes ☒ Potentially – insufficient evidence available; additional information is needed ☐ No	☐ COA can identify differences in scores over time in individuals or groups who have changed with respect to the concept ☒ Other (see Reviewer's comments)	Section 6.3.4.1 ASQoL Evidence Dossier Final (04 September 2018)

Reviewer's comment:

Test-retest reliability was computed examining 12-week and 24-week retest periods. For each no-change anchor (i.e., Patient global impression of change (PGIC), Patient's global assessment of disease activity (PtGADA), and Physicians global assessment of disease activity (PhGADA)) and for each retest period the ICC estimates exceeded the pre-specified criterion of 0.7, except for the 24-week retest period anchored on no change in PtGADA (ICC=0.42).

Known-group analysis conducted by the applicant was inadequate as the known groups defined might not represent subgroups of patients with known and distinct disease severity.

Correlation analysis was used to demonstrate the ASQoL's ability to detect change. While correlation is acceptable, however, ANOVA is generally used as it is a more powerful statistical test.

8 INTERPRETATION OF SCORES

To date, the following information has been submitted (check all that apply):

- ☒ Anchor-based analyses
- ☒ Anchor-based empirical cumulative distribution function (eCDF) curves
- ☐ eCDF study arm curves (Treatment vs. Placebo/Active Comparator)
- ☒ Anchor-based probability density function (PDF) curves
- ☐ PDF study arm curves (Treatment vs. Placebo/Active Comparator)
- ☐ Qualitative support for meaningful change (e.g., patient input)

Table 9 documents the adequacy of the score interpretability of the ASQoL.

Reference ID: 4409249

Table 9. Review of Score Interpretability for ASQoL

COA Attribute	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Score Interpretability	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☐ Appropriate global anchor scales were included for anchor-based analyses ☒ Threshold(s) for within-patient meaningful change identified (anchor-based methods) ☒ Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves) ☐ Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) ☐ Other (see Reviewer's comments)	Section 6.3.4.2 ASQoL Evidence Dossier Final (04 September 2018)

Reviewer's comment:

Based on the results from anchor-based methods and eCDF, the score changes between -0.22 and -0.19 may be considered as the range the score change that represent within-patient meaningful change.

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03/25/2019 09:24:30 PM

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03/25/2019 09:49:28 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 20, 2018

To: Nina Ton, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for CIMZIA (certolizumab pegol) for injection for subcutaneous use (Cimzia)

BLA: 125160 / Supplement 237

In response to DPARP's consult request dated November 2, 2018, OPDP has reviewed the proposed product labeling (PI), carton and container labeling, and medication guide (MG) for CIMZIA (certolizumab pegol) for injection for subcutaneous use (Cimzia). The labeling has been updated as part of the above efficacy supplement for a new indication of non-radiographic axial spondyloarthritis.

PI and MG: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPARP (Nina Ton) on March 5, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed MG were sent under separate cover on March 11, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DPARP (Nina Ton) on March 19, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

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Reference ID: 4406409

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 11, 2019
To:	Sally Seymour, MD Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, Pharm.D., MBA 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, for subcutaneous use
Application Type/Number:	BLA 125160
Supplement Number:	S-237
Applicant:	UCB, Inc.

1 INTRODUCTION

On December 12, 2012, UCB, Inc. submitted for the agency's review an efficacy supplement for the treatment of axial spondyloarthritis (axSpA) including ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). On October 17, 2013 the Agency approved an indication for AS however issued a Complete Response letter for the nr-axSpa indication. On September 28, 2018, UCB, Inc. submitted for the Agency's review a class 2 resubmission for nr-axSpa.

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 Pulmonary, Allergy, and Rheumatology Products (DPARP) on November 5, 2018 and November 2, 2018, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for CIMZIA (certolizumab pegol) for injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft CIMZIA (certolizumab pegol) MG received on September 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 5, 2019.
- Draft CIMZIA (certolizumab pegol) Prescribing Information (PI) received on September 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 5, 2019.

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.

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.

7 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

AMANPREET K SARAI
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 9, 2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 125160/S-237
Product Name and Strength:	Cimzia (certolizumab pegol) For Injection 200 mg/vial Injection 200mg/mL single-dose prefilled syringe
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	UCB, Inc.
FDA Received Date:	September 28, 2018
OSE RCM #:	2018-2184
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sarah K. Vee, PharmD

Reference ID: 4373626

1 REASON FOR REVIEW

This review is in response to DPARP's request for DMEPA to evaluate the proposed carton labeling and prescribing information (PI) submitted by UCB on September 28, 2018. UCB submitted the proposed labeling as a prior approval supplement (PAS) under BLA 125160/S-237 which provides for a new indication, active non-radiographic axial spondyloarthritis (nr-axSpA).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note that the Applicant has added language for the nr-axSpA indication to the inner box vial carton labeling and the PI. We performed a risk assessment of the proposed labeling for areas of vulnerability that may lead to medication errors and did not identify any areas of vulnerability that may lead to medication errors.

4 CONCLUSION & RECOMMENDATIONS

The proposed labeling is acceptable from a medication error perspective.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cimzia received on September 28, 2018 from UCB, Inc..

Table 2. Relevant Product Information for Cimzia	
Initial Approval Date	April 22, 2008
Active Ingredient	Certolizumab pegol
Indication	• 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. • Treatment of adults with non-radiographic axial spondyloarthritis with objective signs of inflammation. (proposed). • Treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Route of Administration	Subcutaneous
Dosage Form	Injection and For Injection
Strength	200 mg/mL (Prefilled Syringe); 200 mg/vial
Dose and Frequency	**Crohn's Disease**: 400 mg initially and at Weeks 2 and 4. If response occurs, follow with 400 mg every four weeks. **Rheumatoid Arthritis**: 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**: 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**: 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. **Non-radiographic Axial Spondyloarthritis:** 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(proposed).

	Plaque Psoriasis: 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.
How Supplied	Lyophilized Powder for Reconstitution: Pack Content 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: 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: 6 alcohol swabs and 6 single use 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.
Storage	Refrigerate carton between 2 to 8 °C (36 to 46 °F). Do not freeze. Protect from light.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 21, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, Cimzia. Our search did not identify any previous relevant reviews.

APPENDIX C. HUMAN FACTORS STUDY

N/A

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Cimzia labels and labeling submitted by UCB, Inc..

- Carton labeling received on September 28, 2018
- Prescribing Information (Image not shown) received on September 28, 2018

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

G.2 Label and Labeling Images

(b) (4)

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/s/

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 1/3/2019

TO: Division of Pulmonary, Allergy and Rheumatology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 125160/S-237

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

(b) (4)

Although OSIS does not have any inspection history for this site, the Requested Review Goal Date is January 25, 2019, which provides insufficient time for the inspection to be completed. Therefore, OSIS declines to conduct an inspection at this site.

(b) (4)

OSIS inspected this site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submission: BLA (b) (4)

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observation: Failure to adhere to criteria for evaluating run acceptability in two runs. Specifically, the data from the original runs should not have been rejected.

After receiving a written response from the sponsor, OSIS recommended that all study data be accepted for Agency review.

In addition, as stated above, the Requested Review Goal Date is January 25, 2019, which provides insufficient time for the inspections to be completed. Therefore, OSIS declines to conduct an inspection at this site.

OSIS would like to bring to the review division's attention that (b) (4) was previously inspected by OSIS in (b) (4) (BLA (b) (4)). The final classification for the inspection was VAI (b) (4)

(b) (4)

Inspection Sites

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	
Analytical		

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125160Origs0237

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125160

MEETING PRELIMINARY COMMENTS

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

Attention: Sandra Bonsall, RAC
Associate Director, Regulatory Affairs

Dear Ms. Bonsall:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Cimzia® (certolizumab pegol).

We also refer to your May 15, 2012, correspondence, received May 15, 2012, requesting a meeting to discuss and seek guidance on Cimzia for the treatment of Psoriatic Arthritis and Axial Spondyloarthritis in support of two supplemental BLAs.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Philantha Montgomery Bowen, MPH, RN
Sr. Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-sBLA

Meeting Date and Time: July 31, 2012; 1:30 -3:00 PM
Meeting Location: White Oak Building 22, Conference Room 1417

Application Number: 125160
Product Name: Cimzia®
Indication: Psoriatic Arthritis and Axial Spondyloarthritis
Sponsor/Applicant Name: UCB, Inc.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **July 31, 2012**, between **UCB, Inc.** and the Division of Pulmonary, Allergy, and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

The purpose of this meeting is to discuss and seek guidance on Cimzia for the treatment of adult patients with active psoriatic arthritis (PsA) and active axial spondyloarthritis (axSpA), including adult patients with active ankylosing spondylitis (AS) in support of two supplemental BLAs. Cimzia is a TNFα blocker and currently approved in the United States for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) and Crohn's disease (CD).

Reference ID: 3165701

The expected outcomes of this meeting are:

- Obtain FDA concurrence on the content and format of the two sBLA filings.
- Provide the FDA with an overview of available data to support the proposed indications.

2. DISCUSSION

2.1. Indication for PsA

***Question 1:* Based on the 09 Feb 2010 FDA written advice, UCB proposes the following indication: treatment of adults with active psoriatic arthritis supported by the American College of Rheumatology 20% criteria (ACR20) response at Week 12, American College of Rheumatology 50% criteria (ACR50), and American College of Rheumatology 70% criteria (ACR70) responses through Week 24.**

UCB understands that the data are ultimately a review issue. However, does the Agency agree in principle that positive results will support the proposed indication?

FDA Response to Question 1: *This approach is generally acceptable; however, support of the proposed indication will depend on the robustness of the data.*

2.2. Clinical Labeling for PsA

***Question 2*: Based on hierarchical testing, UCB plans to include the following clinically important outcomes in the Clinical Studies Section (14.3) of the Cimzia label.**

a. ***Change from Baseline in all individual ACR core components at Weeks 12 [redacted] (b) (4) UCB plans to present the Baseline, Week 12, [redacted] (b) (4) in the label.***

b. ***Change from Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24 to support improvement in physical function. UCB plans to include a brief summary describing the significant improvements in physical function as assessed by the HAQ-DI.***

UCB understands that the data are ultimately a review issue. However, does the Agency agree in principle that positive results will support presentation of these data in the Cimzia label?

FDA Response to Question 2: Your proposal is generally acceptable.

2.3. Clinical and Statistical for PsA

***Question 3*: Does the Agency agree that the imputation method applied in the post-hoc analyses for mTSS is acceptable?**

Reference ID: 3165701

FDA Response to Question 3: You have proposed a different missing data imputation from the planned analyses in PsA001 based on the results of the unblinded data. This will be a review issue.

2.4. Clinical and Statistical for PsA

Question 4: Does the Agency agree that the addition of a minimum time interval between measurements used in the Week 24 post-hoc mTSS analyses is acceptable?

FDA Response to Question 4: We cannot provide you with definitive guidance at this time. We have general concerns about extrapolated data. We are uncertain if 8 weeks is the correct or best minimum time interval between measurements. This will depend on the degree of extrapolation and the proportion of results that are extrapolated from time points less than the prespecified 12 weeks. We are concerned that the treatment effect on radiographic outcomes may be driven by a few extreme observations that disproportionately impact the mean change from baseline in the radiographic score. Thus, the reliability of your data, including the degree to which data has been extrapolated, could affect the acceptability of the results. Additionally, the data are already unblinded. This will be a review issue.

2.5. Statistical –mTSS for PsA001 in prospective Week 48 analysis

Question 5: The second planned sBLA filing for PsA will evaluate the change from Baseline in mTSS at Week 48. All subjects originally randomized to the placebo group were randomized to receive CZP 200mg Q2W or 400mg Q4W in a dose-blinded manner at Week 24. Subjects originally randomized to active treatment remained on their assigned dose regimen. In addition to the Week 48 radiographs, all radiographs from Baseline, Week 12, and Week 24 will be re-read by 2 independent readers who are blinded to the subject treatment and visit sequence. The proposed analysis strategy for subjects with no or only 1 available value to be specified in the Week 48 SAP will be the imputation of the median change from Baseline as described in Question 3 (Section 9.3) and will specify a minimum 8-week window between radiographs that was not included in the Week 24 SAP as described in Question 4 (Section 9.4). It is important to note that structural progression is an objective measure, and the reading of radiographs and analyses will be performed in a blinded fashion.

The planned analyses of mTSS at Week 48 will include placebo-controlled data up to Week 24, followed by dose-blinded data from Week 24 through Week 48. UCB plans to use linear extrapolation from the placebo group up until re-randomization to CZP (Week 16 or Week 24) and compare this extrapolated Week 48 data to the Week 48 data from the 2 treatment arms. This linear extrapolation will be utilized as the primary analytical method. The other sensitivity analyses as described in Question 3, including minimum time window, will also be used for the mTSS efficacy endpoint in the second sBLA filing in PsA.

Does the Agency agree that this approach will be acceptable?

FDA Response to Question 5: Refer to the response to Questions 3 and 4.

Reference ID: 3165701

2.6 Clinical Indication for axSpA

***Question 6**: UCB proposes the following indication: The treatment of adult patients with active axial spondyloarthritis (axSpA), including adult patients with active ankylosing spondylitis (AS) supported by the Assessment in Axial Spondyloarthritis International Society 20% response criteria (ASAS20) at Week 12, as well as ASAS20, Assessment in Axial Spondyloarthritis International Society 40% response criteria (ASAS40), Assessment in Axial Spondyloarthritis International Society response criteria in 5 of 6 domains (ASAS5/6), and ASAS partial remission through Week 24.*

UCB understands that this is ultimately a review issue. However, does the Agency agree in principle that positive results will support the proposed indication?

FDA Response to Question 6: While we understand the clinical utility of the newly defined criteria proposed by the Assessment in Spondyloarthritis International Society (ASAS), we have several concerns from a regulatory standpoint regarding the creation of a new indication based on these criteria. We acknowledge that these concerns represent a change in our previous position.

The newly proposed ASAS criteria for axial SpA define a disease state that represents undifferentiated spondyloarthritis, which if left untreated, might eventually satisfy diagnostic criteria for one of several established diagnoses. While it may be clinically appropriate for the ASAS axial SpA criteria to be more inclusive, from a regulatory standpoint, the axial spondyloarthritis indication is problematic, because it is overly broad and likely to encompass a heterogeneous patient population, including patients for whom the risk-benefit profile of treatment may not be favorable (i.e. patients with chronic mechanical back pain, or patients with transient symptoms that spontaneously remit). Review of your meeting package does not reveal any obvious deficiencies that would preclude filing of a supplemental BLA for the use of Cimzia for the treatment of axial SpA, however, input regarding approvability for Cimzia for an indication of axial SpA would likely require discussion before the Arthritis Advisory Committee.

2.7. Clinical Labeling for axSpA

***Question 7**: Based on hierarchical testing, UCB plans to include the following clinically important outcomes in the Clinical Studies Section (14.4) of the Cimzia label.*

- (b) (4)
- (b) (4)
-

Reference ID: 3165701

FDA Response to Question 7: The proposed indication of axial SpA and the endpoints presented in the product label will likely require discussion in a public forum. Refer to the response to Question 6.

If an indication of axial SpA were to be acceptable, pending review of the results, presentation of change from baseline in ASAS components, BASFI, BASDAI, and BASMI in your product label may be appropriate.. However, it is unlikely that (b) (4) *you propose would be presented in the label.* (b) (4) (b) (4)

2.8. Content for Both Indications

Question 8: a. Based on the FDA written advice dated 09 Feb 2010, UCB has conducted a single study in each indication (PsA and axSpA) to support the sBLA filings. UCB proposes to provide a Clinical Summary of Efficacy in Module 2.7.3 for each sBLA in lieu of an Integrated Summary of Efficacy in Module 5.3.5.

Does the Agency agree with this approach?

FDA Response to Question 8a: Yes, we agree.

b. As noted above, a single study was performed in each indication; therefore, UCB plans to submit the following safety content rather than pool safety information across multiple indications:

- ***An updated RA safety pooling in Module 5.3.5.3 in the PsA sBLA.***
- ***An updated CD safety pooling (cutoff date 16 Jun 2009) in Module 5.3.5 in the PsA sBLA; the data have not previously been submitted to FDA but are displayed and summarized in the Investigator's Brochure that was submitted to IND9869 on 14 Oct 2011.***
- ***Each sBLA will contain a comprehensive summary of indication-specific safety information in Module 2.7.4 with comparisons to the pooled RA safety information.***

- ***Each sBLA will contain a brief summary of the CZP safety profile in CD subjects (Module 2.7.4.5, Safety in Special Groups).***

- ***The PsA sBLA will contain a brief summary of the CZP safety profile in psoriasis subjects (Module 2.7.4.5, Safety in Special Groups).***

Does the Agency agree with this approach?

FDA Response to Question 8b: At this time, your approach appears reasonable. We may have requests for further information or analyses based on review of the submitted data.

2.9. Safety for Both Indications – Exposure and Cutoff Date

Question 9: UCB plans to provide safety exposures through 31 May 2012 for the ongoing PsA001 and AS001 studies.

a. Does the Agency agree with the following proposed strategy for interim analysis and data submission to support the safety of Cimzia in the sBLA filing for the treatment of active PsA?

- ***PsA (study PsA001) safety data for approximately 380 subjects with at least 1 exposure, approximately 360 subjects exposed for at least 24 weeks, and approximately 230 subjects exposed for at least 48 weeks.***

- ***Supportive safety from an updated pooling of 14 RA studies which includes 4049 subjects and 9277 patient-years (Module 5.3.5.3).***

- ***Supportive safety data from 2 psoriasis studies with 117 subjects with at least 1 exposure, 105 subjects exposed for a total of 12 weeks of double-blind treatment, and 62 subjects were exposed for an additional 12 weeks of open-label treatment.***
- ***A report on CZP postmarketing usage from the International Birthdate of Sep 2007 through the cutoff date of 31 May 2012 (Module 5.3.6).***

FDA Response to Question 9a: Your approach is reasonable. However, if a safety signal is noted, further safety data may be required.

b. Does the Agency agree with the following proposed strategy for interim analysis to support the safety of Cimzia in the sBLA filing for the treatment of active axSpA?

- ***axSpA (study AS001) safety data for approximately 299 subjects with at least 1 exposure, approximately 203 subjects exposed for 24 weeks, and approximately 170 subjects exposed for at least 48 weeks.***

- ***Cross-reference to the RA safety pooling in the PsA sBLA.***

Reference ID: 3165701

- ***Cross-reference to the postmarketing report in the PsA sBLA.***

Does the Agency agree with this proposal?

FDA Response to Question 9b: Your approach appears reasonable. However, given the concerns with the axSpA indication as noted in the response to Question 6, whether the safety database that will be provided will support the risk-benefit profile of Cimzia for this indication will be a review issue, and will likely be discussed before an advisory committee.

2.10. Safety for Both Indications - Narratives

Question 10: UCB proposes to provide the following narratives:

- ***The PsA001 and AS001 Week 24 CSRs will contain narratives for subject deaths, premature termination adverse events (PTAEs), and serious adverse events (SAEs).***

- ***Additional PsA001 and AS001 narratives through 31 May 2012 will be discussed in their respective Clinical Summaries of Safety and appended to their respective Week 24 CSRs.***

- ***Of the 14 studies included with the RA safety pooling, the CSRs for the 12 completed studies include full text narratives for subjects with SAEs, PTAEs, and deaths. For the 2 ongoing studies, C87028 and C87051, narrative data listings for subjects with SAEs, PTAEs, and deaths will be provided in the PsA sBLA with cross-reference to this information in the axSpA sBLA. A sample narrative data listing is provided in Attachment 12.5. Does the Agency agree with this proposal?***

FDA Response to Question 10: Your proposal is generally acceptable.

2.11. 120-Day Safety Update for Both Indications

Question 11: Due to the size and supportive nature of the RA safety pooling database, UCB proposes a targeted approach that would refresh the PsA001 and AS001 safety in the 120-Day Safety Update as follows:

- ***Study medication exposure.***

- ***Subject accountability.***

- ***Adverse events (AEs), AE by SOC, SAEs, PTAEs, deaths, markedly abnormal laboratory values, and anti-CZP antibodies.***

- ***Narratives for subjects with SAEs, PTAEs, and deaths.***

Does the Agency agree with this proposal?

FDA Response to Question 11: Your proposal is generally acceptable.

Reference ID: 3165701

2.12. Safety for Both Indications - Narratives

***Question 12*: On 23 Jun 2011, UCB notified the Division that there was a programming error in the Interactive Voice/WEB Response System (IXRS) performed by a vendor. UCB has performed the following measures to ensure that the integrity of the blinding was maintained and that no bias was introduced in PsA001 or AS001:**

- ***Sensitivity analyses which exclude potentially unblinded subjects.***
- ***The IXRS was corrected by UBC on 09 May 2011, and all subsequent notifications contained the correct randomization date at Week 0.***
- ***The potential for unblinding did not occur until Week 16. However, in order to avoid changes to the Week 12 paper CRF pages and any potential impact on the primary variables, the site monitors were instructed to prioritize the collection of the Week 12 CRF pages. The reason for this request was not conveyed to the monitors to avoid potential bias.***

UCB realizes the integrity of the studies will be a review issue; however, does the Agency concur that these corrective actions are adequate?

FDA Response to Question 12: We cannot comment on the adequacy of these corrective actions until the data are reviewed.

2.13. Safety for Both Indications - Narratives

***Question 13*: UCB received feedback on 17 Oct 2011 regarding the proposal to provide Study Data Tabulation Model (SDTM) and Analysis Data model (ADaM) datasets including DDTs and annotated case report forms (CRFs) for the PsA and axSpA sBLA submissions. Based on this, UCB does not plan to create additional .pdf patient profiles.**

Based on the advice received, UCB proposes to provide:

- ***A Reviewer's Guide with the SDTM and ADaM datasets.***
- ***Data Definition files containing a link to the annotated CRFs. The Metadata will include complete information on how the variables were derived.***
- ***The programs used for creating the SDTM, ADaM, and TFL datasets.***

Is this proposal still acceptable to the Agency?

FDA Response to Question 13: Yes. Your approach is acceptable.

Reference ID: 3165701

3.0 GENERAL INFORMATION

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Reference ID: 3165701

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Reference ID: 3165701

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/s/

ANGELA H RAMSEY
07/27/2012