

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125160s215

Trade Name: CIMZIA

Generic or Proper Name: Certolizumab pegol

Sponsor: UCB Inc.

Approval Date: October 17, 2013

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

CENTER FOR DRUG EVALUATION AND RESEARCH

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125160Orig1s215

APPROVAL LETTER



BLA 125160/215

SUPPLEMENT APPROVAL

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 amendments dated February 13, March 8, April 12 and 30, May 16, June 13, August 9, and October 14, 2013.

This Prior Approval supplemental biologics application proposes an indication for the treatment of adult patients with active ankylosing spondylitis.

APPROVAL & LABELING

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 there are too few children with disease/condition to study.

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 package insert(s) to:

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

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. 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, 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

ENCLOSURE:
Content of Labeling

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

/s/

BADRUL A CHOWDHURY
10/17/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125160Orig1s215

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 (1.3)	09/2013
Indications and Usage (1.4)	10/2013
Dosage and Administration (2.3, 2.7)	09/2013
Dosage and Administration (2.4, 2.8)	10/2013
Warnings and Precautions, (5.2, 5.4)	10/2013

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)

DOSAGE AND ADMINISTRATION

CIMZIA is administered by subcutaneous injection. The initial dose of CIMZIA is 400 mg (given as two subcutaneous injections of 200 mg)(2).

Crohn's Disease (2.1)

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

Rheumatoid Arthritis (2.2)

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

Psoriatic Arthritis (2.3)

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

Ankylosing Spondylitis (2.4)

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

DOSAGE FORMS AND STRENGTHS

- For injection: 200 mg lyophilized powder for reconstitution in a single use vial, with 1 mL of sterile Water for Injection (3)
- Injection: 200 mg/mL solution in a single-use prefilled syringe (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 7\%$ and higher than placebo): upper respiratory tract infection, rash, and urinary tract infection (6.1)

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

DRUG INTERACTIONS

- Use with Biological DMARDs – increased risk of serious infections (5.8, 7.1)
- Live vaccines – avoid use with CIMZIA (5.10, 7.2)
- Laboratory tests – may interfere with aPTT tests (7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2013

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*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)*]

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 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. CIMZIA should be brought to room temperature before reconstituting.
- b. Use appropriate aseptic technique when preparing and administering CIMZIA.
- c. Reconstitute the vial(s) of CIMZIA with 1 mL of Sterile Water for Injection, USP using the 20-gauge needle provided.

- d. Gently swirl each vial of CIMZIA without shaking, assuring that all of the powder comes in contact with the Sterile Water for Injection.
- e. Leave the vial(s) undisturbed to fully reconstitute, which may take approximately 30 minutes.
- f. The final reconstituted solution contains 200 mg/mL and should be clear to opalescent, colorless to pale yellow liquid essentially free from particulates.
- g. 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 into 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.

2.6 Preparation and Administration of CIMZIA Using the Prefilled Syringe

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

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

2.7 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.

2.8 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: Lyophilized Powder for Reconstitution

Sterile, white, lyophilized powder for reconstitution and then subcutaneous administration. Each single-use vial provides approximately 200 mg of CIMZIA.

• Injection: Prefilled Syringe

A single-use, 1 mL prefilled glass syringe with a fixed 25 gauge ½ inch thin wall needle, providing 200 mg per 1 mL of CIMZIA.

4 CONTRAINDICATIONS

None.

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 received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating CIMZIA and periodically during therapy.

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

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

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

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. 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.

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.

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, dyspnea, hypotension, rash, serum sickness, and urticaria. Some of these reactions occurred after the first administration of CIMZIA. If such reactions occur, discontinue further administration of CIMZIA and institute appropriate therapy. There are no data on the risks of using CIMZIA in patients who have experienced a severe hypersensitivity reaction towards another TNF blocker; in these patients caution is needed [see *Adverse Reactions (6.1)*].

5.5 Hepatitis B Virus Reactivation

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

Test patients for HBV infection before initiating treatment with CIMZIA. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with CIMZIA should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy.

In patients who develop HBV reactivation, discontinue CIMZIA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV

reactivation is controlled is not known. Therefore, exercise caution when considering resumption of CIMZIA therapy in this situation and monitor patients closely.

5.6 Neurologic Reactions

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

5.7 Hematological Reactions

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

Although no high risk group has been identified, exercise caution in patients being treated with CIMZIA who have ongoing, or a history of, significant hematologic abnormalities. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on CIMZIA. Consider discontinuation of CIMZIA therapy in patients with confirmed significant hematologic abnormalities.

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

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

5.9 Autoimmunity

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

5.10 Immunizations

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

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

5.11 Immunosuppression

Since TNF mediates inflammation and modulates cellular immune responses, the possibility exists for TNF blockers, including CIMZIA, to affect host defenses against infections and malignancies. The

impact of treatment with CIMZIA on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood [see *Warnings and Precautions (5.1, 5.2, 5.5) and Adverse Reactions (6.1)*]. The safety and efficacy of CIMZIA in patients with immunosuppression has not been formally evaluated.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The most serious adverse reactions were:

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

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 ($\geq 8\%$) 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 $\geq 5\%$ 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 $\geq 3\%$ 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.

Infections

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

The incidence of new cases of infections in controlled clinical studies in rheumatoid arthritis was 0.91 per patient-year for all CIMZIA-treated patients and 0.72 per patient-year for placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, herpes infections, urinary tract infections, and lower respiratory tract infections. In the controlled rheumatoid arthritis studies, there were more new cases of serious infection adverse reactions in the CIMZIA treatment groups, compared to the placebo groups (0.06 per patient-year for all CIMZIA doses vs. 0.02 per patient-year for placebo). Rates of serious infections in the 200 mg every other week dose group were 0.06 per

patient-year and in the 400 mg every 4 weeks dose group were 0.04 per patient-year. Serious infections included tuberculosis, pneumonia, cellulitis, and pyelonephritis. In the placebo group, no serious infection occurred in more than one subject. There is no evidence of increased risk of infections with continued exposure over time [see *Warnings and Precautions (5.1)*].

Tuberculosis and Opportunistic Infections

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

The majority of cases occurred in countries with high endemic rates of TB. Reports include cases of miliary, lymphatic, peritoneal, as well as pulmonary TB. The median time to onset of TB for all patients exposed to CIMZIA across all indications was 345 days. In the studies with CIMZIA in RA, there were 36 cases of TB among 2,367 exposed patients, including some fatal cases. Rare cases of opportunistic infections have also been reported in these clinical trials. [see *Warnings and Precautions (5.1)*].

Malignancies

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

Heart Failure

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

Autoantibodies

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

In clinical trials of TNF blockers, including CIMZIA, in patients with RA, some patients have developed ANA. Four patients out of 2,367 patients treated with CIMZIA in RA clinical studies developed clinical signs suggestive of a lupus-like syndrome. The impact of long-term treatment with CIMZIA on the development of autoimmune diseases is unknown [see *Warnings and Precautions (5.9)*].

Immunogenicity

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

The overall percentage of patients with antibodies to certolizumab pegol detectable on at least one occasion was 7% (105 of 1,509) in the rheumatoid arthritis placebo-controlled trials. Approximately one third (3%, 39 of 1,509) of these patients had antibodies with neutralizing activity *in vitro*. Patients treated with concomitant immunosuppressants (MTX) had a lower rate of antibody development than patients not

taking immunosuppressants at baseline. Patients treated with concomitant immunosuppressant therapy (MTX) in RA-I, RA-II, RA-III had a lower rate of neutralizing antibody formation overall than patients treated with CIMZIA monotherapy in RA-IV (2% vs. 8%). Both the loading dose of 400 mg every other week at Weeks 0, 2 and 4 and concomitant use of MTX were associated with reduced immunogenicity.

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

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

Hypersensitivity Reactions

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

6.2 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

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 Category B

Risk Summary

Adequate and well-controlled studies with CIMZIA have not been conducted in pregnant women.

Certolizumab pegol plasma concentrations obtained from 10 women treated with CIMZIA during pregnancy and their newborn infants demonstrated low placental transfer of certolizumab pegol. CIMZIA may be eliminated at a slower rate in exposed infants than in adult patients. No fetal harm was observed in animal reproduction studies. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to CIMZIA during pregnancy. To enroll, healthcare providers or patients can call 1-877-311-8972.

Human Data

In an independent clinical study conducted in 10 pregnant women with Crohn's disease treated with CIMZIA, certolizumab pegol concentrations were measured in maternal blood as well as in cord and infant blood (n=12) at the day of birth. The last dose of CIMZIA (400 mg for every mother) was given on average 19 days prior to delivery (range 5-42 days). Plasma certolizumab pegol concentrations were <0.41 –1.66 µg/mL in cord blood, <0.41 – 1.58 µg/mL in infant blood, and 1.87–59.57 µg/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 µg /mL over 4 weeks suggesting that CIMZIA may be eliminated at a slower rate in infants than adults.

Animal Data

Because certolizumab pegol does not cross-react with mouse or rat TNF α , reproduction studies were performed in rats using a rodent anti-murine TNF α pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol. Reproduction studies have been performed in rats at doses up to 100 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to cTN3 PF.

8.3 Nursing Mothers

It is not known whether certolizumab pegol is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from

CIMZIA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Due to its inhibition of TNF α , CIMZIA administered during pregnancy could affect immune responses in the *in utero*-exposed newborn and infant. Although certolizumab pegol levels were low in 12 infants exposed to CIMZIA *in utero*, the clinical significance of these low levels is unknown. Additional data available from one exposed infant suggests that CIMZIA may be eliminated at a slower rate in infants than in adults [see *Use in Specific Populations (8.1)*]. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

8.5 Geriatric Use

Clinical studies of CIMZIA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Population pharmacokinetic analyses of patients enrolled in CIMZIA clinical studies concluded that there was no apparent difference in drug concentration regardless of age. Because there is a higher incidence of infections in the elderly population in general, use caution when treating the elderly with CIMZIA [see *Warnings and Precautions (5.1)*].

10 OVERDOSAGE

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

11 DESCRIPTION

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

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Certolizumab pegol binds to human TNF α with a KD of 90pM. TNF α is a key pro-inflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralizes TNF α (IC₉₀ of 4 ng/mL for inhibition of human TNF α in the *in vitro* L929 murine fibrosarcoma cytotoxicity assay) but does not neutralize lymphotoxin α (TNF β). Certolizumab pegol cross-reacts poorly with TNF from rodents and rabbits, therefore *in vivo* efficacy was evaluated using animal models in which human TNF α was the physiologically active molecule.

Certolizumab pegol was shown to neutralize membrane-associated and soluble human TNF α in a dose-dependent manner. Incubation of monocytes with certolizumab pegol resulted in a dose-dependent inhibition of LPS-induced TNF α and IL-1 β 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 TNF α 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. TNF α stimulates the production of downstream inflammatory mediators, including interleukin-1, prostaglandins, platelet activating factor, and nitric oxide. Elevated levels of TNF α have been implicated in the pathology of Crohn's disease and rheumatoid arthritis. Certolizumab pegol binds to TNF α , inhibiting its role as a key mediator of inflammation. TNF α is strongly expressed in the bowel wall in areas involved by Crohn's disease and fecal concentrations of TNF α 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 TNF α levels are found in the synovial fluid of rheumatoid arthritis patients and play an important role in the joint destruction that is a hallmark of this disease.

12.3 Pharmacokinetics

• Absorption

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

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

Following subcutaneous administration, peak plasma concentrations of certolizumab pegol were attained between 54 and 171 hours post-injection. Certolizumab pegol has bioavailability (F) of

approximately 80% (ranging from 76% to 88%) following subcutaneous administration compared to intravenous administration.

- **Distribution**

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

- **Metabolism**

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

- **Elimination**

PEGylation, the covalent attachment of PEG polymers to peptides, delays the metabolism and elimination of these entities from the circulation by a variety of mechanisms, including decreased renal clearance, proteolysis, and immunogenicity. Accordingly, certolizumab pegol is an antibody Fab' fragment conjugated with PEG in order to extend the terminal plasma elimination half-life ($t_{1/2}$) of the Fab'. The terminal elimination phase half-life ($t_{1/2}$) was approximately 14 days for all doses tested. The clearance following IV administration to healthy subjects ranged from 9.21 mL/h to 14.38 mL/h. The clearance following sc dosing was estimated 17 mL/h in the Crohn's disease population PK analysis with an inter-subject variability of 38% (CV) and an inter-occasion variability of 16%. Similarly, the clearance following sc dosing was estimated as 21.0 mL/h in the RA population PK analysis, with an inter-subject variability of 30.8% (%CV) and inter-occasion variability 22.0%. The route of elimination of certolizumab pegol has not been studied in human subjects. Studies in animals indicate that the major route of elimination of the PEG component is via urinary excretion.

- **Special Populations**

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

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

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

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

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

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

- **Drug Interaction Studies**

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

Formal drug-drug interaction studies have not been conducted with CIMZIA upon concomitant administration with corticosteroids, nonsteroidal anti-inflammatory drugs, analgesics or 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 TNF α , reproduction studies were performed in rats using a rodent anti-murine TNF α 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 to 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 (CDAI¹) of 220 to 450 points, inclusive. CIMZIA was administered subcutaneously at a dose of 400 mg in both studies. Stable concomitant medications for Crohn's disease were permitted.

Study CD1

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

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

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

Timepoint	% Response or Remission (95% CI)	
	Placebo (N = 328)	CIMZIA 400 mg (N = 331)
Week 6		
Clinical Response [#]	27% (22%, 32%)	35% (30%, 40%)*
Clinical Remission [#]	17% (13%, 22%)	22% (17%, 26%)
Week 26		
Clinical Response	27% (22%, 31%)	37% (32%, 42%)*
Clinical Remission	18% (14%, 22%)	29% (25%, 34%)*
Both Weeks 6 & 26		
Clinical Response	16% (12%, 20%)	23% (18%, 28%)*
Clinical Remission	10% (7%, 13%)	14% (11%, 18%)
* p-value < 0.05 logistic regression test		
[#] Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points		

Study CD2

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

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

Table 3 Study CD2 - Clinical Response and Clinical Remission

	% Response or Remission (95% CI)	
	CIMZIA 400 mg x3 + Placebo N = 210	CIMZIA 400 mg N = 215
Week 26		
Clinical Response [#]	36% (30%, 43%)	63% (56%, 69%)*
Clinical Remission [#]	29% (22%, 35%)	48% (41%, 55%)*
* p < 0.05		
[#] Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points		

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

14.2 Rheumatoid Arthritis

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

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

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

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

Clinical Response

The percent of CIMZIA-treated patients achieving ACR20, 50, and 70 responses in Studies RA-I and RA-IV are shown in Table 4. CIMZIA-treated patients had higher ACR20, 50 and 70 response rates at 6 months compared to placebo-treated patients. The results in study RA-II (619 patients) were similar to the results in RA-I at Week 24. The results in study RA-III (247 patients) were similar to those seen in study RA-IV. Over the one-year Study RA-I, 13% of CIMZIA-treated patients achieved a major clinical response, defined as achieving an ACR70 response over a continuous 6-month period, compared to 1% of placebo-treated patients.

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

Response	Study RA-I Methotrexate Combination (24 and 52 weeks)			Study RA-IV Monotherapy (24 weeks)		
	<u>Placebo + MTX</u> <u>N=199</u>	<u>CIMZIA^(a) 200 mg + MTX q 2 weeks</u> <u>N=393</u>	<u>CIMZIA^(a) 200 mg + MTX - Placebo + MTX</u> <u>(95% CI)^(d)</u>	<u>Placebo</u> <u>N=109</u>	<u>CIMZIA^(b) 400 mg q 4 weeks</u> <u>N=111</u>	<u>CIMZIA^(b) 400 mg - Placebo</u> <u>(95% CI)^(d)</u>
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%)	[Redacted]	

^(a) CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4

^(b) CIMZIA administered every 4 weeks not preceded by a loading dose regimen

^(c) Major clinical response is defined as achieving ACR70 response over a continuous 6-month period

^(d) 95% Confidence Intervals constructed using the large sample approximation to the Normal Distribution.

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

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

^(a) CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4

^(b) CIMZIA administered every 4 weeks not preceded by a loading dose regimen

^(c) Study RA-I - Visual Analog Scale: 0 = best, 100 = worst. Study RA-IV - Five Point Scale: 1 = best, 5 = worst

^(d) Patient Assessment of Arthritis Pain. Visual Analog Scale: 0 = best, 100 = worst

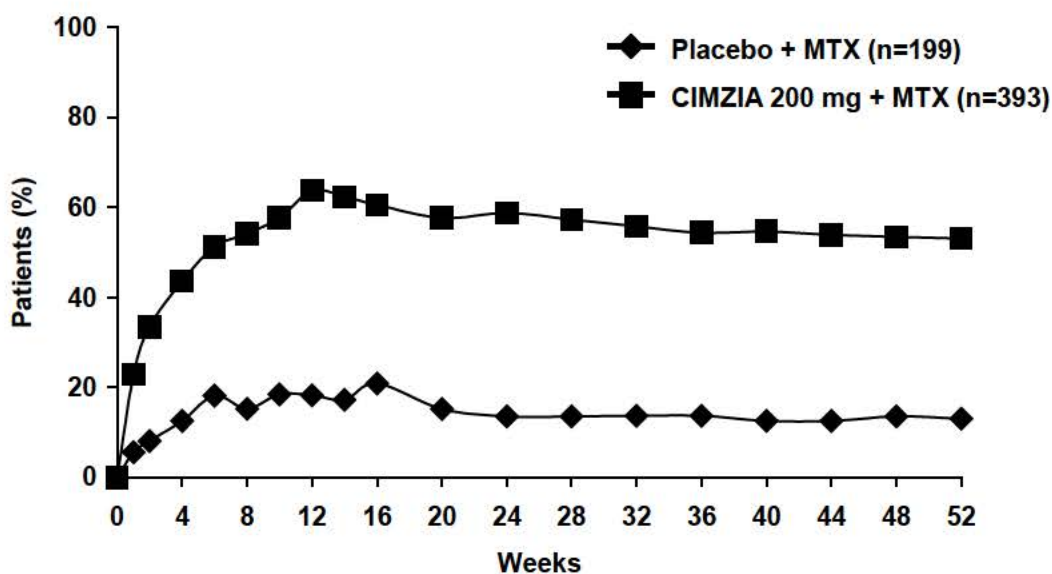
^(e) Health Assessment Questionnaire Disability Index; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

All values are last observation carried forward.

[†]For Study RA-I, median is presented. For Study RA-IV, mean (SD) is presented except for CRP which presents geometric mean

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

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



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

Radiographic Response

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

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

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

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

Physical Function Response

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

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 7. 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 8.

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. However, the safety and efficacy of CIMZIA in the treatment of patients with plaque psoriasis has not been established.

Table 7: ACR Responses in Study PsA001 (Percent of Patients)

Response ^(c)	Placebo	CIMZIA ^(a) 200 mg Q2W	CIMZIA ^(b) 400 mg Q4W
	N=136	N=138	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 8: Components of ACR Response in Study PsA001

Parameter	Placebo ^(c)		CIMZIA ^(a) 200 mg Q2W		CIMZIA ^(b) 400 mg Q4W	
	N=136	N=136	N=138	N=138	N=135	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

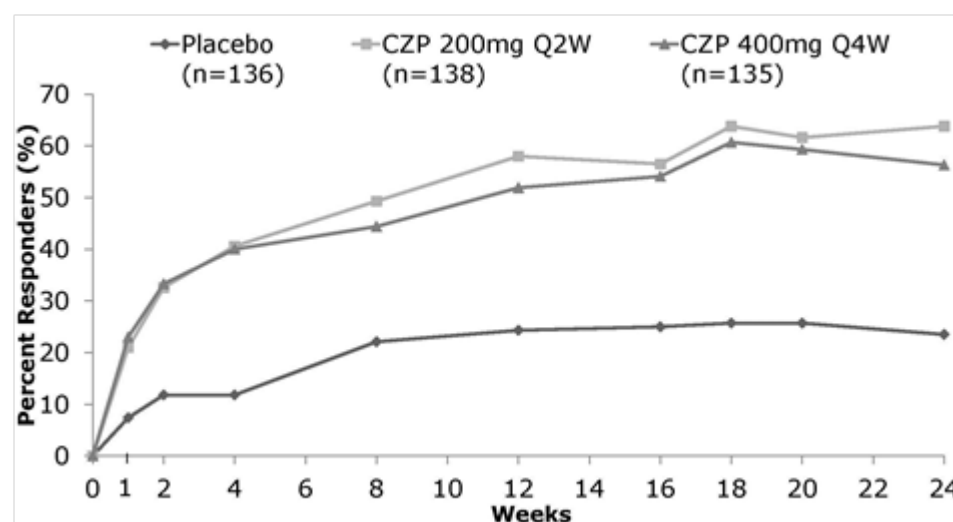
^(g) The HAQ-DI, 4 point scale 0=without difficulty and 3=unable to do

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 200mg every 2 weeks or 400mg every 4 weeks achieved ASAS 20 response compared to AS patients treated with placebo (Table 9). 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 10.

Table 9: ASAS Responses in AS patients at Weeks 12 and 24 in study AS-1

Parameters	Placebo N=57	CIMZIA ^(a) 200mg every 2 weeks N=65	CIMZIA ^(b) 400mg 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 10: 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) 200mg every 2 weeks N=65		CIMZIA ^(b) 400mg 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

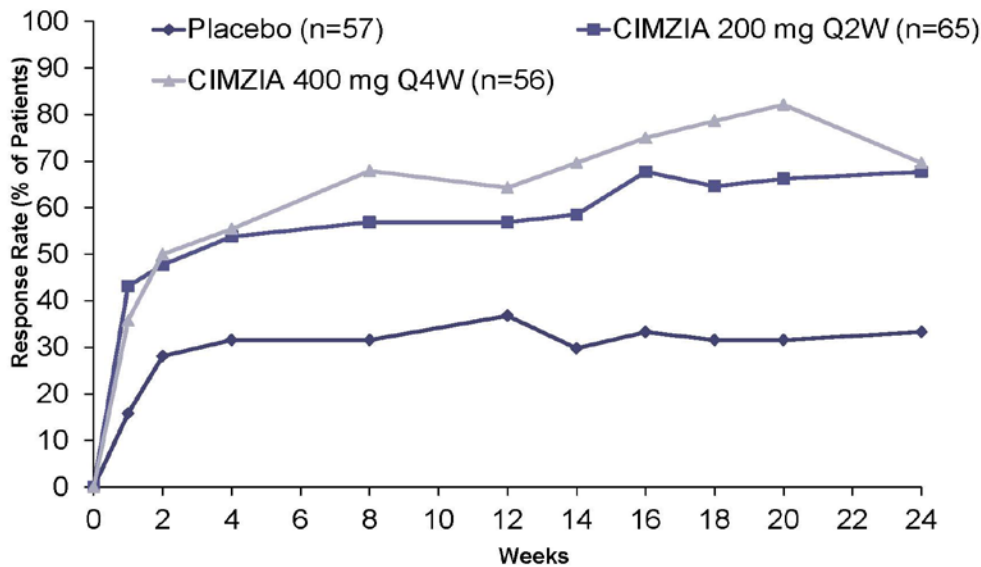
^(d)BASDAI is Bath Ankylosing Spondylitis Disease Activity Index

^(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.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Storage and Stability

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

- **Lyophilized Powder for Reconstitution:**

NDC 50474-700-62

Pack Content

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

- **Prefilled Syringe**

NDC 50474-710-79

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

- **Prefilled Syringe Starter Kit**

NDC 50474-710-81

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.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 Patient Counseling

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

- **Immunosuppression**

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

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

- **Allergic Reactions**

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

- **Other Medical Conditions**

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

17.2 Instruction on Prefilled Syringe Self-Injection Technique

After proper training by a qualified healthcare professional in subcutaneous injection technique, a patient may self inject with CIMZIA using the Prefilled Syringe if a healthcare provider determines that it is appropriate. A patient's ability to administer CIMZIA subcutaneous injections should be checked to ensure correct administration. Suitable sites for injection include the thigh or abdomen. CIMZIA should be injected when the liquid is at room temperature.

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

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

disposal technique. Actively discourage any reuse of the injection materials.

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

US License No. 1736

Medication Guide
CIMZIA® (CIM-zee-uh)
(certolizumab pegol)

lyophilized powder or solution for subcutaneous use

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

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

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

- Your 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.

You should not start receiving CIMZIA if you have any kind of infection unless your healthcare provider says it is okay.

Before you receive CIMZIA, tell your healthcare provider if you:

° Think you have an infection, flu-like symptoms, or have any other symptoms of an infection such as:

- fever, sweat, or chills
 - muscle aches
 - cough
 - shortness of breath
 - blood in phlegm
 - weight loss
 - warm, red, or painful skin or sores on your body
 - diarrhea or stomach pain
 - burning when you urinate or urinate more often than normal
 - feeling very tired
- are being treated for an infection
 - get a lot of infections or have infections that keep coming back
 - have diabetes, HIV, 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, lived in, or traveled to countries where there is more risk for getting TB. Ask your healthcare provider if you are not sure.
- live or have lived in certain parts of the country (such as the Ohio and Mississippi River valleys) where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis). These infections may develop or become more severe if you take CIMZIA. If you do not know if you have lived in an area where histoplasmosis, coccidioidomycosis, or blastomycosis is common, ask your healthcare provider.
- have or have had hepatitis B
- use the medicine Kineret® (anakinra), Orencia® (abatacept), Rituxan® (rituximab), or Tysabri® (natalizumab)

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

Certain types of Cancer

- There have been cases of unusual cancers in children and teenage patients using TNF-blocking agents.
- For people taking TNF-blocker medicines, including CIMZIA, the chances of getting lymphoma or other cancers may increase.
- People with RA, especially more serious RA, may have a higher chance for getting a kind of cancer called lymphoma.

What is CIMZIA?

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

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

What should I tell my healthcare provider before starting treatment with CIMZIA?

CIMZIA may not be right for you. Before starting CIMZIA, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection. (See, “What is the most important information I should know about CIMZIA?”)
- have or have had any type of cancer.
- have congestive heart failure.
- have seizures, any numbness or tingling, or a disease that affects your nervous system such as multiple sclerosis.
- are scheduled to receive a vaccine. Do not receive a live vaccine while taking CIMZIA.
- are allergic to any of the ingredients in CIMZIA. See the end of this Medication Guide for a list of the ingredients in CIMZIA.
- are pregnant or planning to become pregnant. It is not known if CIMZIA will harm your unborn baby. Tell your healthcare provider right away if you become pregnant while receiving CIMZIA.

Pregnancy Registry: If you become pregnant while taking 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. It is not known if CIMZIA passes into your breast milk. You and your healthcare provider should decide if you will receive CIMZIA or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Especially tell your healthcare provider if you take the following medicines due to a higher chance for serious infections:

- Kineret[®] (anakinra), Orencia[®] (abatacept), Rituxan[®] (rituximab), or Tysabri[®] (natalizumab).
- medicines called Tumor Necrosis Factor (TNF) blockers such as Remicade[®] (infliximab), Humira[®] (adalimumab), Enbrel[®] (etanercept), or Simponi[®] (golimumab).

Ask your healthcare provider if you are not sure.

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

How should I receive CIMZIA?

- CIMZIA comes as lyophilized powder or as a solution in a prefilled syringe for injection.
- If your healthcare provider prescribes the CIMZIA powder, your CIMZIA should be injected by a healthcare provider. Each dose of CIMZIA will be given as 1 or 2 separate injections under the skin in your stomach area 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 the right way to inject CIMZIA.
- Read the detailed Instructions for Use booklet 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 is given by an injection under the skin. 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.
- CIMZIA may be injected into your stomach or upper thighs. If you are prescribed more than 1 injection, each injection should be given at a different site in your stomach or upper thighs.
- Make sure the solution in the prefilled syringe is clear to colorless to light yellow. The solution should be mostly free from particles. **Do not use the CIMZIA prefilled syringe if the medicine looks cloudy or if there are large or colored particles.**
- Do not miss any doses of CIMZIA. If you miss a dose, call your healthcare provider or pharmacist for instructions.
- Make sure to keep all follow-up appointments with your healthcare provider.

What are the possible side effects of CIMZIA?

CIMZIA can cause serious side effects including:

- See “What is the most important information I should know about CIMZIA?”
- **Heart Failure** including new heart failure or worsening of heart failure you already have. Symptoms include shortness of breath, swelling of your ankles or feet, or sudden weight gain.
- **Allergic Reactions.** Signs of an allergic reaction include a skin rash, swelling or itching of the face, tongue, lips, or throat, or trouble breathing.
- **Hepatitis B virus reactivation in patients who carry the virus in their blood.** In some cases patients have died as a result of hepatitis B virus being reactivated. Your doctor should monitor you carefully before and during treatment with CIMZIA to see if you carry the hepatitis B virus in your blood. Tell your doctor if you have any of the following symptoms:
 - feel unwell
 - skin or eyes look yellow
 - tiredness (fatigue)
 - poor appetite or vomiting
 - pain on the right side of your stomach (abdomen)
- **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
 - numbness or tingling
 - problems with your vision
 - 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 doesn't go away, bruising or bleeding very easily, or looking very pale.
- **Immune reactions including a lupus-like syndrome.** Symptoms include shortness of breath, joint pain, or a rash on the cheeks or arms that worsens with sun exposure.

Call your 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)

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

These are not all of the possible side effects of CIMZIA. For more information, ask your healthcare provider or pharmacist.

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 36°F to 46°F (2°C to 8°C).
- 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.

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

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

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.

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

Product manufactured by:

UCB, Inc.

1950 Lake Park Drive

Smyrna, GA 30080

US License No. 1736

Revised: October 2013

Instructions for Use
CIMZIA® (CIM-zee-uh)
(certolizumab pegol)
solution for subcutaneous use
Prefilled Syringes

Read this Instructions for Use booklet that comes with CIMZIA before you start receiving it, and before each injection of CIMZIA. This Instructions for Use booklet does not take the place of talking with your healthcare provider about your medical condition or treatment. These instructions are for 1 injection only. You may need more than 1 injection at a time depending on your prescribed dose of CIMZIA.

Do not share your CIMZIA Prefilled Syringe with needle attached with another person. You may give another person an infection or get an infection from them.

Supplies you will need to give your CIMZIA injection: See Figure A and Figure B.

- 1 CIMZIA prefilled syringe with needle attached. You may need 2 CIMZIA prefilled syringes with needles attached to give higher doses.
- 1 or 2 alcohol swabs
- 1 or 2 clean cotton balls or gauze pads
- 1 puncture-resistant sharps disposal container. See “Disposal of your syringes with needles attached” at the end of this Instructions for Use booklet.

CIMZIA comes in a tray containing 2 prefilled glass syringes. Use a new CIMZIA syringe for each injection.



Figure A

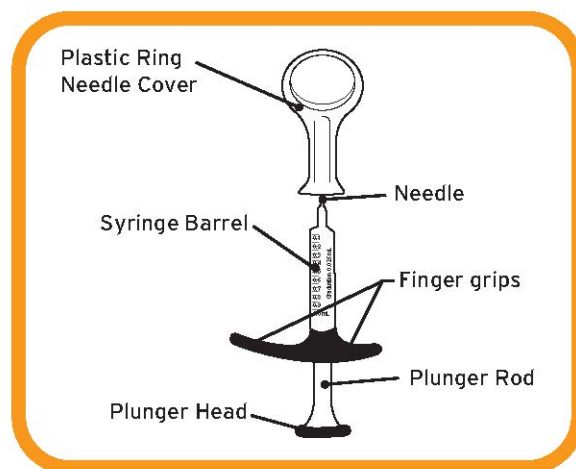


Figure B

Setting up for your CIMZIA injection:

Step 1.

Take the carton containing the prefilled syringes of CIMZIA out of the refrigerator. Check the expiration date on the syringe carton and label. See **Figure C**.

If the expiration date has passed, **do not** use the syringe. Call your pharmacist for questions about the expiration date. Do not use if the tamper evident seals are missing or broken on the top and bottom of the carton when you receive it. If this is the case, contact your pharmacist.

Step 2.

Remove the prefilled syringe from the box and let it warm to room temperature. Do not warm the syringe in any other way. If you are not using the second syringe, put the carton containing the remaining prefilled syringe back in the refrigerator.

Step 3.

Find a clean, flat work surface, such as a table.

Step 4.

Make sure the liquid medicine in the prefilled syringe is clear to pale yellow and free from particles.. **Do not** inject the medicine if it is cloudy or discolored. Call your healthcare provider or pharmacist if you have any questions about your CIMZIA prefilled syringe.

Step 5.

Gather all the supplies you will need for your injection.

Step 6.

Wash your hands with soap and warm water and dry thoroughly with a clean towel.



Figure C

Selecting and preparing your injection site:

Step 7.

Choose your injection site(s) on your stomach or upper thighs. **See Figure D.**

- Choose a new injection site each time you use CIMZIA.
- Each new injection should be given at least 1 inch from the site you used before. If you choose your stomach, avoid the 2 inches around your belly button (navel).
- Do not inject into areas where your skin is tender, bruised, red or hard, or where you have scars or stretch marks.
- Change injection sites between your stomach and upper thighs to reduce the chance of having a skin reaction.
- You may want to write down the site you use for your injection to help you remember to use a different site each time you inject.

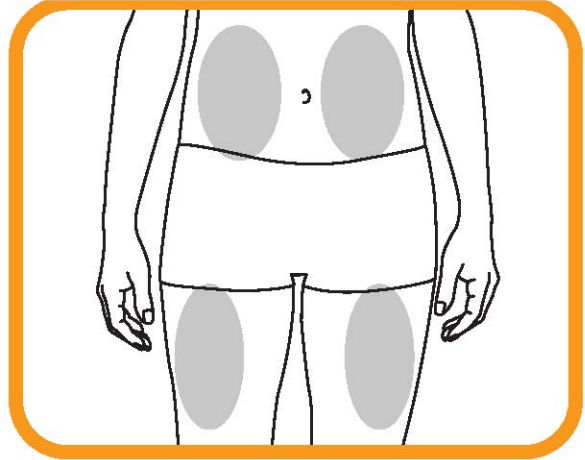


Figure D

Step 8.

Clean your injection site with an alcohol swab. Let the area dry completely.

Giving your CIMZIA injection:

Step 9.

Pick up the prefilled syringe with 1 hand and hold it with the needle pointing up. With your other hand, remove the needle cover by pulling straight up on the plastic ring. **See Figure E.**

Do not touch the needle and do not let the needle touch any surface.
Place the needle cover to the side.

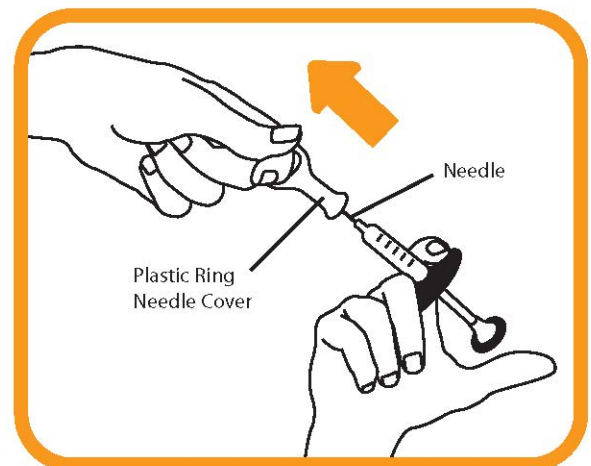


Figure E

Step 10. Hold the syringe so the needle is pointing up. Lightly tap the syringe to push any small air bubbles to the top. **See Figure F.**

Gently push the plunger slowly to remove any bubbles. Stop pushing the plunger when all of the air bubbles are gone.

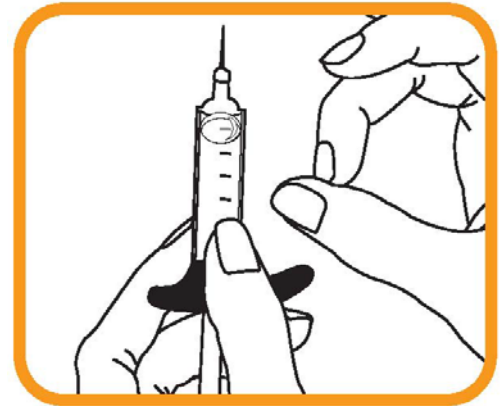


Figure F

Step 11. Hold the syringe in 1 hand. With your other hand, gently pinch a fold of skin at the cleaned injection site. **See Figure G.**

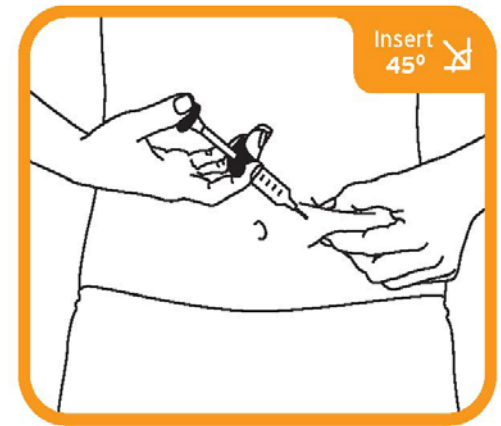


Figure G

Step 12. With a quick, “dart-like” motion, insert the needle into your skin at about a 45 degree angle. Release the pinched skin, keeping the syringe in position. Slowly push on the plunger all the way down until the syringe is empty. **See Figure H.**

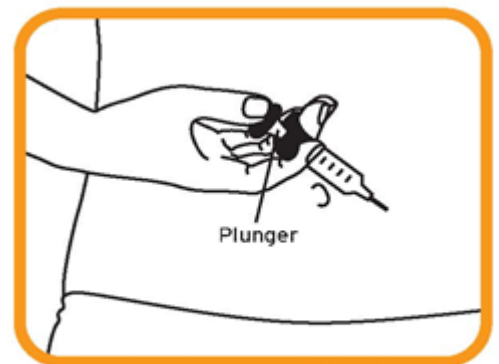


Figure H

Step 13.

When the syringe is empty, pull the needle out of your skin while carefully keeping the needle at the same angle as inserted.

See Figure I.

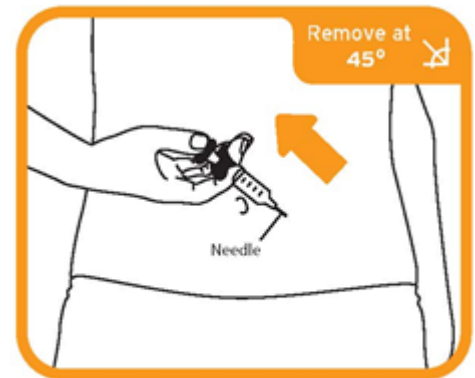


Figure I

Step 14.

Place a dry cotton ball or gauze pad over the injection site for several seconds. See Figure J.

Do not rub the injection site. Do not use an alcohol swab as it may cause stinging. If there is a little bleeding, cover the injection site with a small bandage.

To avoid a needle-stick injury, do not try to recap the needle.

Do not reuse any of your injection supplies.

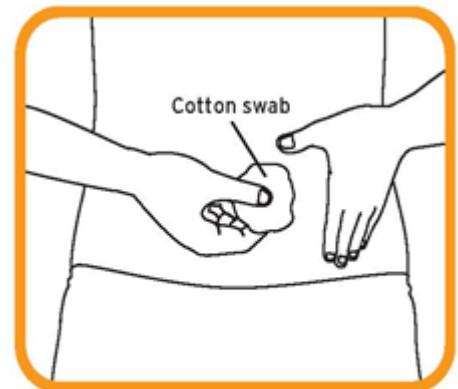


Figure J

Disposal of your syringes with needles attached:

- Put your used syringes with needle attached in a FDA-cleared sharps disposal container right away after use. **See Figure K.**

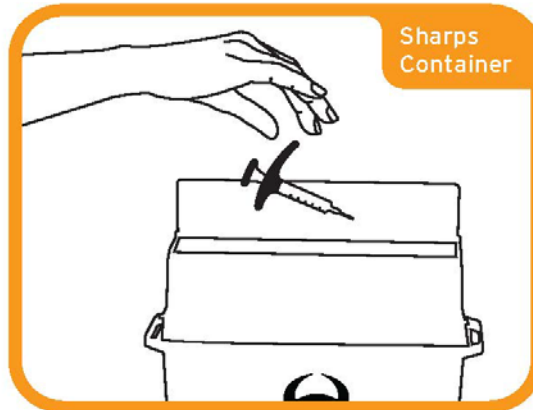


Figure K

Do not throw away (dispose of) loose syringes and needles in your household trash.

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
 - upright and stable during use
 - leak-resistant
 - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Product manufactured by:

UCB, Inc.

1950 Lake Park Drive

Smyrna, GA 30080

Revised: 10/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125160Orig1s215

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 those with non-radiographic axial spondyloarthritis (NR Axial SpA) (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.

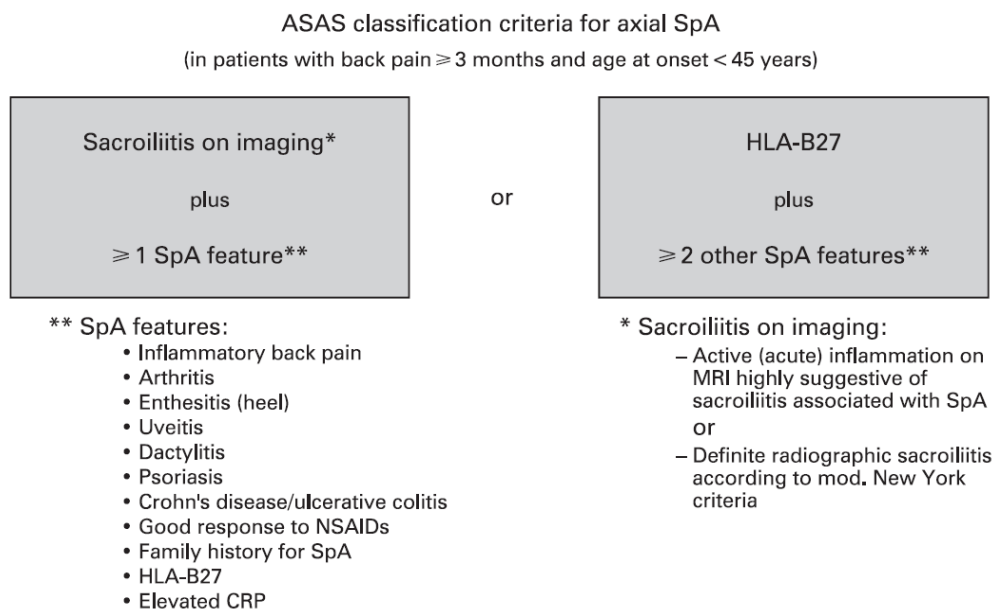
⁴ Amor B, Dougados M, Mijiyawa M. Criteria of the classification of spondyloarthropathies. *Rev Rheum Mal Osterartic* 1990; 57: 85-89.

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



Sensitivity 82.9%, specificity 84.4%; n = 649 patients with chronic back pain and age at onset < 45 years. Imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and a specificity of 97.3%.

** Note: Elevated CRP is considered a SpA feature in the context of chronic back pain

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 spondyloarthritis 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 with positive inflammatory markers.
- 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) with objective signs of inflammation (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 patients with active non-radiographic axial spondyloarthritis (b) (4) objective signs of inflammation (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), or in patients with NR Axial SpA (b) (4) with objective signs of inflammation (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:

125160Orig1s215

OFFICER/EMPLOYEE LIST

Officer/Employee List
sBLA 125160/215 Cimzia

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Adeleye, Adewale

Brar, Satjit S

Buenconsejo, Joan

Chowdhury, Badrul

Duer, Robin

Hulett, Melissa

Kim, Yongman

Jafari, Ladan

Maynard, Janet

Merchant, Lubna

Muthukkumar, Subramanian

Ton, Nina

Yim, Sarah

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125160Orig1s215

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. <i>Approval for ankylosing spondylitis, with revisions to proposed labeling</i> 2. <i>Complete response for other axial spondyloarthritis</i>

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-TNF α 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

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 ≥ 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

otherwise have debilitating disease. Thus ASAS developed criteria for the classification of axial spondyloarthritis² 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

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 ≥ 4 (out of 10), spinal pain ≥ 4 (out of 10), elevated c-reactive protein (CRP), or sacroiliitis on magnetic resonance imaging (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

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.

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 ≥ 4 (out of 10), spinal pain ≥ 4 (out of 10), elevated c-reactive protein (CRP), or sacroiliitis on magnetic resonance imaging (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.

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

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

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.

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-

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).

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 proposed "Treatment of adults with active (b) (4) non-radiographic axial SpA (b) (4) objective signs of inflammation (u) (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:

"Treatment of adults with active ankylosing spondylitis (AS). (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. (b) (4)

It is possible that this subgroup could be a minority fraction of the 98 confirmed nr-axSpA patients in AS001. 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:

125160Orig1s215

MEDICAL REVIEW(S)

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, all 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 Criteria¹ 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

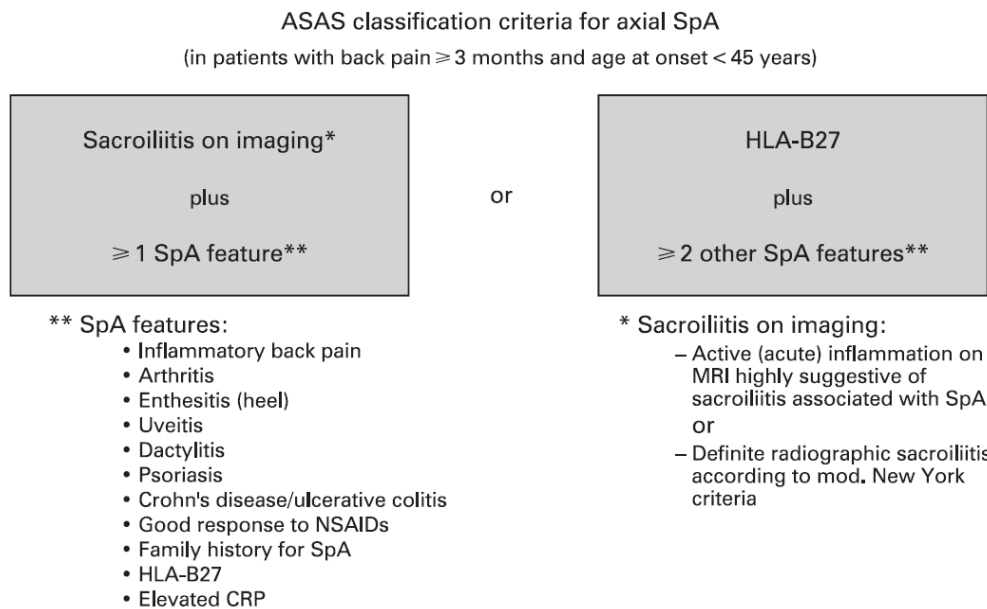
Source: van der Linden S. Arthritis Rheum 1984;27(4):361-8.

The modified New York Criteria¹ 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



Sensitivity 82.9%, specificity 84.4%; n = 649 patients with chronic back pain and age at onset $<$ 45 years. Imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and a specificity of 97.3%.

** Note: Elevated CRP is considered a SpA feature in the context of chronic back pain

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 etiologies⁵. 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 treatment⁵⁻¹⁰. 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 ASAS 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 States¹³. 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 active (b) (4) non-radiographic axial SpA (b) (4) (b) (4) objective signs of

inflammation

(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).

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	Serious infections, including bacterial sepsis, tuberculosis, invasive fungal infections, histoplasmosis, and other opportunistic infections Malignancies, including hepatosplenic T-cell lymphoma, lymphoma, and other malignancies in children and adolescents
Warnings/Precautions	- Infections - Hepatitis B reactivation - Invasive fungal infections - Malignancies - Hepatotoxicity - Hypersensitivity disorders - Demyelinating disorders (e.g., multiple sclerosis) - Adverse outcomes in patients with heart failure - Pancytopenia, leukopenia, neutropenia, thrombocytopenia - Autoimmune disorders (e.g., lupus-like syndrome) - Infusion-related reactions/Injection-site reactions

[†] All TNF-inh bitor 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.

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 (CFR) 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 TNF α 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.

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.

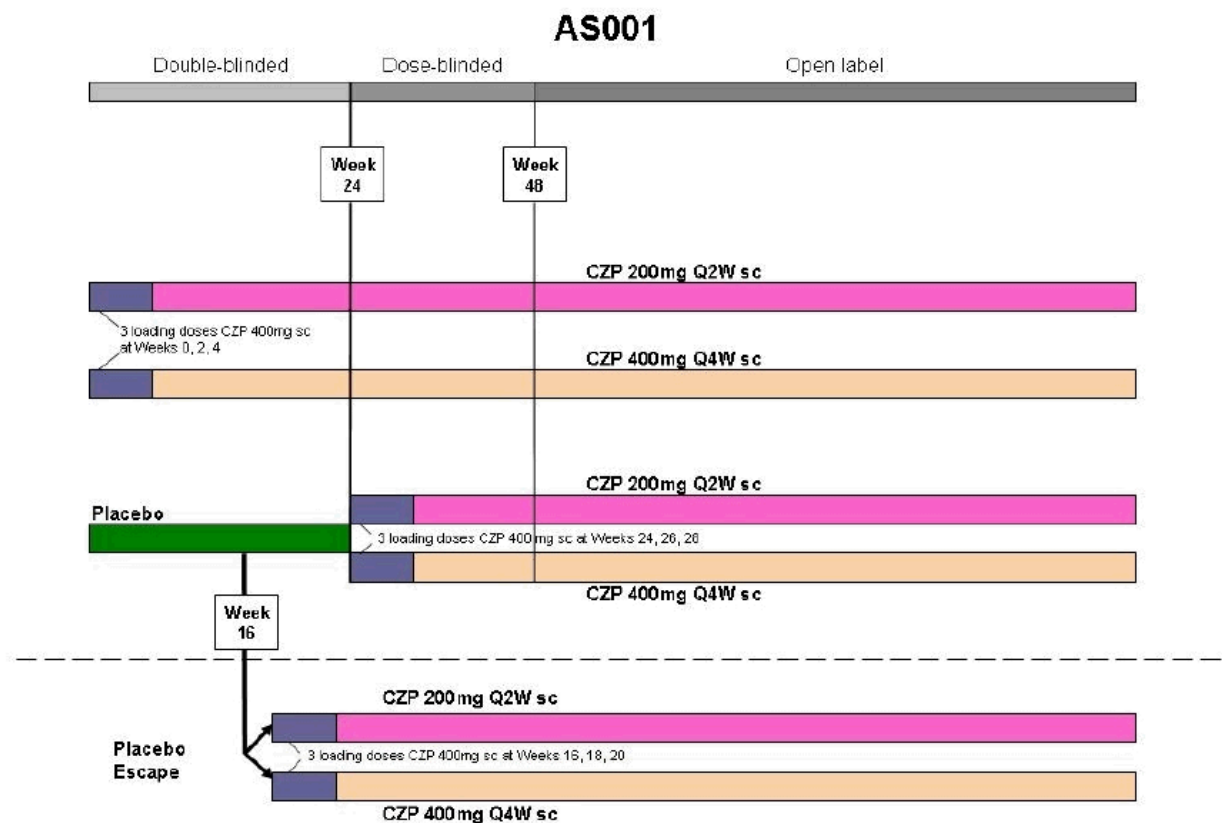
Overall Design of Trial AS001: Trial AS001 was a multicenter, randomized, double-blind, placebo-controlled trial of certolizumab in adult patients with active axial SpA. The trial included 5 periods:

- 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 imaging 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.

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 ≤ 10 mg 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 ≤ 3 g daily HCQ ≤ 400 mg daily MTX ≤ 25 mg 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=hydroxychloroquine; 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 ≥ 5 mm 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*, *Coccidioides*, *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 $> 2 \times$ ULN, creatinine $> \text{ULN}$ or WBC $< 3.0 \times 10^9/\text{L}$).
 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 ≤ 10 mg 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 ≤ 3 g daily; HCQ ≤ 400 mg daily; MTX ≤ 25 mg 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

Clinical Review
 Janet Maynard, MD, MHS
 BLA 125160/215
 Certolizumab (Cimzia®) for axial spondyloarthritis (axial SpA)

Protocol Activity	Scr ^a	BL	Weeks																												SFU ^d				
			-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	
BASMI & Spinal mobility ^a	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	X	X	X	X
BASDAI	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	X	X	X	X
BASFI		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	X	X	X
SF-36		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	X	X
AsQoL		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	X	X	X
MOS Sleep Scale		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	X	X
EQ-5D		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	X	X
MASES		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	X	X	X
Total & nocturnal spinal pain		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	X	X	X
Subject's Global assessment		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	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	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	X	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	X	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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGIC										X																									
CZP plasma concentration &		X	X	X	X				X	X																							X ^r	X	X

Protocol Activity	Scr ^a -5 to -1	BL 0	Weeks																																
			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 H ^b	Every 4 wks ^c	Every 12 wks ^c	158 or W/D	SFU ^d			
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	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	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	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 ^b	X	X	X	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

$S=(21.1\text{cm}-A)/2.1\text{cm}$	For the lateral lumbar flexion (mean right/left)
$S=(A-8\text{cm})/3\text{cm}$	For the tragus-to-wall distance (mean right/left)
$S=(7.4-A)/0.7\text{cm}$	For the lumbar flexion (modified Schober)

$S=(124.5\text{cm}-A)/10\text{cm}$	For the maximal intermalleolar distance
$S=(89.3^\circ-A)/8.5^\circ$	For the cervical rotation (mean right/left)
Always with the additional condition $0 \leq S \leq 10$	

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 through 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:

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 $\alpha=0.05$.

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 $\alpha=0.05$; if the null hypothesis was rejected, the next hypothesis in the sequence was to be tested at $\alpha=0.05$; 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 active (b) (4) non-radiographic axial SpA (b) (4) (b) (4) objective signs of inflammation (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.

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.

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

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 units 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), patient 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.”

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.

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-glutamyltransferase 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 assess 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 examination¹¹ 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 (12.6)	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 11 th 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

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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 indication "active (b) (4)
non-radiographic axial SpA (b) (4)
objective signs of inflammation (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 (b) (4)
the division disagreed with inclusion of the proposed (b) (4)

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 (b) (4) As previously noted, the division disagreed (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 [REDACTED] (b) (4)
[REDACTED] for inclusion in the label were removed. (u) (v)

7. [REDACTED] (b) (4)
[REDACTED] 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/

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125160Orig1s215

CHEMISTRY REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Food and Drug Administration

Center for Drugs Evaluation and Research

DATE: September 10, 2013

TO: File for STN: 125160/213 and 215
RPM: Andrew Shiber

FROM: Subramanian Muthukkumar Ph.D.,
Product Reviewer, DMA/OBP/CDER, HFD-123

THROUGH: Rashmi Rawat, Ph.D.
Team Leader, DMA/OBP/CDER, HFD-123

Sarah Kennett, Ph.D.
Review Chief
DMA/OBP/CDER, HFD-123

APPLICANT: UCB, Inc.
Contact Person: Sandra Bonsall, Director, US Regulatory affairs
Tel: (770) 970-8591

PRODUCT: Cimzia® (certolizumab-pegol/CDP870)-Recombinant humanized monoclonal antibody to TNF- α . Lyophilized powder or solution for injection 200 mg/mL

SUBJECT: 1. STN: 125160/213 Supplemental Biologic License Application (sBLA) for the treatment of adults with active Psoriatic Arthritis (PsA).
2. STN: 125160/215 Supplemental Biologic License Application (sBLA) for the treatment of adults with active Axial Spondyloarthritis (axSpa).

DATE OF RECEIPT: STN: 125160/213- November 29, 2012
STN: 125160/215- December 17, 2012

ACTION DUE DATE: STN: 125160/213- September 29, 2013
STN: 125160/215- October 17, 2013

REVIEW RECOMMENDATION: *Information provided in the supplements to support the categorical exclusion from the requirement to file an Environmental Assessment for CDP870 per 21CFR §25.31 (c) is adequate and deemed acceptable. I therefore recommend approval of supplements 125160/213 and 125160/215.*

Summary: BLA 125160 was approved on April 22, 2008 for Crohn’s disease and May 13, 2009 for Rheumatoid Arthritis. Supplements #213 and #215 are Supplemental Biologic License Applications (sBLAs) for the treatment of Psoriatic Arthritis (PsA) and Axial Spondyloarthritis (axSpa), respectively. This review covers a summary of previously submitted immunogenicity assay information and the environmental assessment sections provided in the current sBLA supplements. Information provided in these sections is considered appropriate. Please refer below for detail.

Review of environmental assessment: An environmental assessment section has been provided in both the submissions. In Section 1.12.14, the Sponsor requested a categorical exclusion from the requirement to file an Environmental Assessment for CDP870 per 21CFR §25.31 (c). CDP870 is a humanized antibody Fab' fragment-polyethylene glycol (PEG) conjugate composed of naturally occurring amino acids. Thus UCB justified that this product is in compliance with the categorical exclusion criteria of 21 CFR 25.31(c). UCB further stated that no extraordinary circumstances exist which require submission of an Environmental Assessment. Information related to inactivation of waste streams during product manufacture and a toxicological review of PEG and PEGylated polypeptides is provided in BLA125160/80. UCB also indicated that PEGs are practically non-toxic, with no adverse effects observed in rats at levels of 2% in the diet (approximately equivalent to 1000mg/kg bw/day). The maximum amount of PEG2MAL expected to be used in the manufacture of CDP870 drug substance per year is (b) (4).

Reviewer’s Comment: *Information provided to support the categorical exclusion from the requirement per 21CFR §25.31 (c) is considered adequate.*

Review of immunogenicity: In the original BLA (STN 125160) submission, immunogenicity of certolizumab-pegol was evaluated by a double-antigen sandwich (bridge) ELISA. Anti-certolizumab pegol antibodies are captured from plasma by immobilized certolizumab pegol; the anti-certolizumab pegol antibodies are then detected by biotin-labeled certolizumab pegol, which binds to the free binding arm on the captured antibody. The assay is completed with horseradish peroxidase-streptavidin followed by substrate. Based on the original BLA review, the immunogenicity assay information provided was considered adequate to detect anti-certolizumab pegol antibodies.

As per discussion with the Clinical Pharmacology Reviewer, Liang Zhao, no update on immunogenicity data is required from the clinical pharmacology perspective, because there is no dedicated clinical pharmacology studies included in either of the current sBLA supplements.

FUTURE INSPECTION ITEMS: None

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125160Orig1s215

ENVIRONMENTAL ASSESSMENT



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Memorandum
Food and Drug Administration
Center for Drugs Evaluation and Research

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DATE OF RECEIPT: STN: 125160/213- November 29, 2012
STN: 125160/215- December 17, 2012

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STN: 125160/215- October 17, 2013

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FUTURE INSPECTION ITEMS: None

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125160Orig1s215

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: sBLA STN 125160
supplement# 215

Drug Name: CIMZIA® (certolizumab pegol)

Indication(s): For reducing signs and symptoms in adult patients with active axial spondyloarthritis, including ankylosing spondylitis

Applicant: UCB, Inc.

Date(s): Submitted: December 14, 2012
PDUFA: October 14, 2013

Review Priority: Standard

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Yongman Kim, Ph.D.

Concurring Reviewers: Joan Buenconsejo, Ph.D.

Medical Division: Division of Pulmonary, Allergenic, and Rheumatology Products

Clinical Team: Janet Maynard, M.D.
Sarah Yim, M.D.

Project Manager: Nina Ton

Keywords: Clinical studies, new indication, sensitivity analyses

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1. EXECUTIVE SUMMARY

UCB provided data from study AS001 to support the use of certolizumab pegol at the doses of 200 mg every two weeks or 400 mg every 4 weeks to treat ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) under the umbrella of axial spondyloarthritis (axSpA). Subjects enrolled in the study had active axial SpA based on the Assessment of Spondyloarthritis International Society (ASAS) axSpA classification criteria and had an inadequate response to or intolerance to at least one NSAID. The study was designed to enroll an equal number of AS and nr-axSpA patients, thus ensuring representation of the entire axSpA population while allowing comparison between axSpA subgroups. 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. The primary endpoint was the proportion of responders to ASAS20 response criteria at Week 12.

Based on my review of the data and study report, the study provided a robust data supporting the efficacy of CZP meeting the pre-specified study success criterion: superiority of CZP to placebo in terms of ASAS20 response in the overall axSpA populations. Significant differences were also observed in each of the subpopulation (AS and nr-axSpA). The magnitude of effect was consistent across the subpopulations and what was observed in the overall axSpA population. These efficacy findings were consistent in both AS and nr-axSpA subpopulations regardless of the discrepancy in pelvic x-ray readings at local or central lab for modified New York criteria. The magnitude of effect in ASAS20 response for the AS population ranged from 17% to 20% between CZP 200 mg every two weeks and placebo, and ranged from 23% to 27% between the CZP 400 mg every 4 weeks and placebo. The magnitude of effect in ASAS20 response for the nr-axSpA population ranged from 19% to 23% between CZP 200 mg every two weeks and placebo, and about 23% between the CZP 400 mg every 4 weeks and placebo.

The direction of the difference in each of the components of the ASAS response criteria was consistent with the result of the primary endpoint. Treatment differences in favor of CZP were also significant for all four ranked secondary endpoints at Week 12 and Week 24. A higher proportion of patients in the certolizumab pegol arms achieved ASAS20 response and the change from baseline was greater in the CZP arms for BASFI, BASDAI, and BASMI compared to placebo.

The Arthritis Advisory Committee convened on July 23, 2013 to discuss the efficacy and safety of certolizumab pegol. The 14-member committee discussed the efficacy of treatment on signs and symptoms of active axSpA, including AS as well as potential safety signals. The committee voted 8 to 5 with 1 abstention that the efficacy had been demonstrated for signs and symptoms in patients with active axSpA, including patients with AS. The committee voted 13 to 1 that the available data for safety were adequate. Overall, they voted 7 to 6 for approval with 1 abstention.

2. INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Certolizumab pegol (CZP, hereafter) is a recombinant, humanized monoclonal anti-TNF α antibody Fab' fragment produced by *Escherichia coli*, which is linked to polyethylene glycol (PEG).

In April 2008, certolizumab pegol was approved for Crohn's disease in the United States (US). In May 2009, certolizumab pegol was approved for Rheumatoid Arthritis (RA) in the United States (US).

The current submission is seeking for approval of certolizumab pegol in reducing signs and symptoms in adult patients with active axial spondyloarthritis, including patients with ankylosing spondylitis.

2.1.2 History of Drug Development and Regulatory Interactions

The following are study milestones with regulatory interactions:

- IND meeting held (9 February 2010)
- Study started (9 April 2010)
- Data cut-off for primary analysis (14 January 2012)
- Statistical Analysis Plan (SAP) finalized (22 March 2012)
- Pre-sBLA meeting held (13 June 2012)
- sBLA submitted (14 December 2012)
- Arthritis Advisory Committee meeting held (23 July 2013)

In the IND meeting in 2010, the clinical development program for axial SpA was discussed between the applicant and the Division. The Division provided the applicant with advices mainly on the clinical aspects of the studies.

In the finalized statistical analysis plan (SAP) before database lock, the handling of missing values for continuous secondary endpoints was addressed by applying last observation carried forward (LOCF) imputation and multiplicity concern was addressed by using a fixed sequence of key secondary endpoints. Further, we agreed with the approach to handle missing data for the primary endpoint, that is, patients who withdrew for any reason will be assigned as non-responder. Although we previously agreed with the LOCF approach to impute missing data, this is not something we will agree now. We will not agree to a single-value imputation that assumes

patients' scores at the time of drop out will be the same at the end of the study, particularly when the reason for dropout is treatment-related. Since only 16 patients (5%) withdrew before week 12 and only a fraction was due to adverse events, the impact of missing data is not much of a concern. Nonetheless, additional analyses were conducted by the applicant to assess the impact of missing data on results from the analyses of continuous endpoints (i.e., ASAS components and secondary endpoints).

2.1.3 Major Statistical Issues

During the review of the clinical study, several statistical issues that warrant further exploration of data and discussion in the review were identified. Some of the issues were resolved. Some key issues are highlighted below:

1. Impact of missing data:

The impact of missing data was not prominent because missing binary endpoints such as ASAS20 were treated conservatively using non-responder imputation. Missing continuous endpoints including ASAS20 components were imputed by the last observation carried forward (LOCF). Since only about 5 percent of all patients withdrew prior to Week 12, the concern on LOCF imputation on the analyses was not important. Refer to Section 3.2.3.

2. Multiplicity adjustment for the secondary endpoints, the two CZP dose groups, and the pre-specified subgroup analyses on AS and nr-axSpA subpopulation:

The secondary endpoints were tested in a hierarchical fixed sequence approach to properly control the type I error rate. The hierarchical test was also intended to handle multiple comparisons between two CZP dose regimens and placebo. Refer to Section 3.2.3.

Although the applicant did not plan to adjust for AS and nr-axSpA subgroup analyses, it was specified in the protocol that they will conduct efficacy analyses on the subgroups. Since the statistically significant results were consistent in overall and each subpopulation, my initial concern was mitigated. Refer to Section 3.2.3.

3. Unblinding to assign rescue medication to placebo non-responders after escape:

Regarding placebo patients who took escape treatment, my concern was mitigated since they took the escape treatment after Week 12 of primary analysis time point and remained until Week 24 for most secondary analysis time point. It is highly likely that these placebo patients' efficacy scores will get better and comparisons with CZP group would be closer to the null. Refer to Section 3.2.3.

4. Discrepancy between x-ray readings between local & central lab:

The applicant identified differences in the local interpretation of screening sacroiliac x-rays and central interpretation of baseline sacroiliac x-rays. At screening, 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 assessed by a central reader. A high proportion of patients were reclassified when x-rays were evaluated centrally rather than locally. Of the 178 patients who were classified as having AS by local investigators, 29 of them (16%) were felt not to have definitive sacroiliitis when x-rays were evaluated centrally (Table 7). Of the 147 patients who were classified as having nr-axSpA by local investigators, 72 of them (49%) were considered by the central readers to have sacroiliitis on baseline x-rays. Based on baseline central reader's assessment, 184 patients had AS and 98 patients had nr-axSpA in this trial.

These issues will be discussed further in the section 3.2.

2.2 Data Sources

sBLA 125160 was submitted on December 14, 2012 and can be found in the electronic document room (EDR) of the Center for Drug Evaluation and Research. The study report including protocols, statistical analysis plan, and all referenced literature can be found in the EDR. SAS codes used in statistical analyses and the electronic SAS data sets with raw and derived variables and data definitions were provided in the EDR using the following path:

[\\cbsap58\mleCTD_Submissions\STN125160\125160.enx](#)

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, I was able to reproduce the primary and key secondary efficacy analyses. No noticeable deviations between CRFs and analysis datasets relevant to primary and key secondary endpoints were found. Also I verified the randomized treatment assignments.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The study AS001 employed randomized, multi-center, placebo-controlled, parallel-group, double-blind design. The study consists of three phases (Figure 1): 24 weeks of double-blind period, 24 weeks of dose-blind period, and 110 weeks of open-label extension period. There were 128 participating investigational sites in North America, Latin America, Western Europe, and Central/Eastern Europe.

At the start of the double-blind period, 325 subjects were randomized to placebo (107 subjects) or CZP 200mg Q2W (111 subjects) or CZP 400mg Q4W (107 subjects). 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.

Subjects receiving placebo who did not achieve at least a minimal response (defined as those subjects who did not achieve ASAS20 response criteria) at both Weeks 14 and 16 were allocated to escape treatment (randomized in a 1:1 ratio to receive CZP 200mg Q2W or CZP 400mg Q4W) from Week 16 onwards.

The study was designed to enroll an equal number of AS and nr-axSpA patients, thus ensuring representation of the entire axSpA population while allowing comparison between axSpA subgroups. Of note, classification into these subgroups varied depending on whether x-rays were evaluated by local investigators or central assessors.

Figure 1: Study Design

Source: Adapted from the study protocol, 5.3 Schematic diagram (page 32).

The primary endpoint was the proportion of responders to ASAS20 response criteria at Week 12. 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 (PTGADA)
- Pain assessment (the total spinal pain NRS score)
- Function (represented by BASFI)
- Inflammation (the mean 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 in Bath Ankylosing Spondylitis Functional Index (BASFI) to Weeks 12 and 24, change in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) to Weeks 12 and 24, change in Bath Ankylosing Spondylitis Metrology Index (BASMI) to Weeks 12 and 24. Therefore, other analyses than primary analysis and secondary analyses specified above are to be treated as exploratory from a regulatory perspective and are discouraged to be included in the label.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Enrolled in the study were patients with both active AS and nr-axSpA who had an inadequate response to or intolerance to ≥ 1 NSAID, or had a contraindication for NSAIDs, as defined by the investigator. AS patients met the ASAS classification criteria for axial SpA and fulfilled the modified New York criteria for AS. Nr-axSpA patients also met the ASAS classification criteria for axial SpA, but did not fulfill the modified New York criteria for AS. A total of 325 subjects (overall axSpA population or ITT population) were enrolled in this study. There were 178 AS patients and 147 nr-axSpA patients. The following charts describe the patient disposition for Overall axSpA population (Figure 2) and AS subpopulation (Figure 3).

Figure 2: Patient Disposition (Overall axSpA population)

▼
26
Comple
Wk24

Source: Adapted from the clinical study report, figure 7-1 (page 106).

Figure 3: Patient Disposition (AS subpopulation)

13
Comple
Wk2.

Source: Adapted from the clinical study report, figure 7-2 (page 107).

Following are my findings regarding disposition from the database and these are consistent with the applicant's report.

- Overall axSpA population :
 - 325 were randomized to placebo (107) or CZP 200mg (111) or CZP 400mg (107)
 - 309 (95%) remained at Week 12 (98 placebo, 108 CZP 200mg, 103 CZP 400mg)
 - 300 (92%) remained at Week 24 (97 placebo, 105 CZP 200mg, 98 CZP 400mg)
 - 25 (8%) withdrew (10 placebo, 6 CZP 200mg, 9 CZP 400mg)
 - 7 due to AE (2 placebo, 2 CZP 200mg, 3 CZP 400mg)
 - 56 (52%) placebo escaped
- AS subpopulation :
 - 178 were randomized to placebo (57) or CZP 200mg (65) or CZP 400mg (56)
 - 169 (95%) remained at Week 12 (53 placebo, 63 CZP 200mg, 53 CZP 400mg)
 - 165 (93%) remained at Week 24 (53 placebo, 60 CZP 200mg, 52 CZP 400mg)
 - 13 (7%) withdrew (4 placebo, 5 CZP 200mg, 4 CZP 400mg)
 - 5 due to AE (1 placebo, 2 CZP 200mg, 2 CZP 400mg)
 - 30 (53%) placebo escaped

The primary efficacy analysis was conducted on the intent-to-treat (ITT) population. The ITT set included all randomized patients who took at least one study drug.

There were no noticeable imbalances of the demographics and baseline characteristics between treatment groups (Table 1, Table 2).

Overall, the average age of patients was 40 years, 62% male, 90% Caucasian, 16% prior anti-TNF α user, and the average disease duration was 7 years. The average weight was about 82 kg.

Table 1: Demographic Characteristics (ITT)

Asian
American Indian/Alaskan Na
Native Hawaiian or Pacific Islander
Other/Mixed
Missing

BMI class (kg/m³), n
≤18.5
18.5 - <25
25 - <30
≥30

Source: Adapted from the clinical study report, table 7-1 (pages 109-110).

Table 2: Baseline Medical Characteristics (ITT)

Testing for HLA-B2 (%)
Negative
Positive
Missing

Baseline BASDAI score FAS, mean (SD)
Baseline BASMI line: scores, FAS, mean (SD)
Baseline BASFI score FAS, mean (SD)

Adapted from the clinical study report, table 7-6 (pages 124-125).

3.2.3 Statistical Methodologies

The Wald test was used in the analysis of dichotomous endpoints including the primary ASAS20 response and other secondary endpoints.

The analysis of covariance (ANCOVA) was used in the analysis of change from baseline of continuous endpoints adjusting for the stratification factors of region, modified NY criteria, and prior anti-TNF α use applied at randomization. The baseline value of the continuous variables was included as a covariate.

To control the type I error rate, the secondary endpoints were tested in a hierarchical fixed sequence approach. The hierarchical test was also intended to handle multiple comparisons between two CZP dose regimens and placebo. Each endpoint in the sequence must be significant ($p < 0.05$) in order for the subsequent endpoint in the chain to be considered significant:

1. ASAS20 response at Week 12 for CZP 200mg Q2W
2. ASAS20 response at Week 12 for CZP 400mg Q4W
3. ASAS20 response at Week 24 for CZP 200mg Q2W
4. ASAS20 response at Week 24 for CZP 400mg Q4W
5. Change from Baseline in BASFI at Week 12 for CZP 200mg Q2W and CZP 400mg Q4W combined
6. Change from Baseline in BASDAI at Week 12 for CZP 200mg Q2W and CZP 400mg Q4W combined
7. Change from Baseline in BASFI at Week 24 for CZP 200mg Q2W and CZP 400mg Q4W combined

- Q4W combined
8. Change from Baseline in BASDAI at Week 24 for CZP 200mg Q2W and CZP 400mg Q4W combined
 9. Change from Baseline in BASMI at Week 12 for CZP 200mg Q2W and CZP 400mg Q4W combined
 10. Change from Baseline in BASMI at Week 24 for CZP 200mg Q2W and CZP 400mg Q4W combined.

To handle missing data in the primary analysis, patients who withdrew for any reason were assigned as non-responder. Regarding placebo patients who took escape treatments, my concern was mitigated since they took the escape treatments after Week 12 of primary analysis time point and remained till the of Week 24 for most secondary analysis time point, implying that these placebo patients' efficacy scores got better and comparisons with CZP group would be conservative. For the continuous missing endpoints, LOCF was used. Although we previously agreed in applying LOCF to impute missing data, this is not something we would agree to now. We would not agree to a single-value imputation that assumes patients' scores at the time of drop out will be the same at the end of the study. Since only 16 patients (5%) withdrew before week 12 and only a fraction was due to adverse events, the impact of missing data is not much of a concern. Nonetheless, additional analyses were conducted by the applicant and by me to assess the impact of missing data on results from the analyses of continuous endpoints (i.e., ASAS components and secondary endpoints).

The applicant conducted several subgroup analyses based on demographics and baseline characteristics – age group (<45, ≥45), sex, race (white, non-white), symptom duration (≤5 years, >5 years), prior anti-TNF α use (yes, no), baseline DMARD use (yes, no), baseline CRP category (≤15mg/L, >15mg/L). I added subgroup analyses based on region (America, Europe).

3.2.4 Results and Conclusions

In the overall axial SpA population (ITT), significantly more patients in the CZP 200mg Q2W and in the CZP 400mg Q4W achieved ASAS20 response at Week 12 compared to placebo (19% and 25%, respectively). There was a small numerical difference in ASAS20 response between CZP 200 mg Q2W and 400 mg Q4W (58% and 64%, respectively). Sixteen patients (5%) who were randomized but withdrew prior to Week 12 were not influential, and inclusion or exclusion of these patients in the analyses did not change the magnitude of effect and the overall conclusion. To see if any interaction between treatment and strata of AS and nr-axSpA subpopulations, the logistic regression was conducted testing for the interaction. There was no significant interaction between treatment and the subpopulations (Table 4).

Table 3: ASAS20 Response Rates at Week 12 – Overall axSpA Population (ITT NRI)

	N	n	Response Rate	Difference vs. PBO (95% CI)	P-value
PBO	107	41	38%		
CZP 200mg Q2W	111	64	58%	19% (6%, 32%)	0.004
CZP 400mg Q4W	107	68	64%	25% (12%, 38%)	<0.001

Note: P-values based on Wald test & CIs based on normal approximation.

CZP=certolizumab; PBO=placebo; ITT=intent-to-treat; NRI=Non-responder imputation was applied to missing data; axSpA= axial spondyloarthritis

Table 4: Logistic Regression Analysis on ASAS20 Response at Week 12 (ITT NRI)

	Odds Ratio	95% CI for Odds Ratio	P-value
N=325			
Treatment Comparison (reference = PBO, n = 107)*			
CZP 200mg Q2W, n=111	2.30	(1.31, 4.04)	0.004
CZP 400mg Q2W, n=107	2.80	(1.58, 4.96)	<0.001
CZP combined, n=218**	0.97	(0.78, 1.23)	0.817

Note: * Logistic regression model with factors of region, modified NY criteria, and prior anti-TNF α use.

** Logistic regression model with factors of strata of AS & nr-axSpA and **interaction of treatment by strata** of AS & nr-axSpA.

CZP=certolizumab; PBO=placebo; ITT=intent-to-treat; NRI=Non-responder imputation was applied to missing data

The significant finding in the overall axSpA population indicates that CZP reduced signs and symptoms of axial SpA. As discussed in Dr. Maynard’s review, 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 clinically important to determine if the magnitude of the treatment effect was similar in these subgroups.

Although the subgroup analyses were not part of the hierarchy for multiple testing, these subgroup analyses were pre-specified in the protocol. Without adjustment for multiplicity, except for the comparison between CZP200 mg Q2W and placebo in the nr-axSpA, significant differences were also observed in each of the subpopulation (Table 5). The magnitude of effect was consistent across subgroups. The differences in proportion of ASAS20 response in the CZP 200 mg Q2W and CZP 400 Q4W compared to placebo were 19% and 23%, respectively in the nr-axSpA population, and 20% and 27%, respectively in the AS population. This is consistent with what was observed in the overall population.

The direction of the difference in each of the components of the ASAS response criteria -- Patient's Global Assessment of Disease Activity, Total Back Pain, Bath Ankylosing Spondylitis Functional Index, and Inflammation (Mean of Q5 & Q6 on BASDAI Scale), was consistent with the result of the primary endpoint (Table 6) for the overall population and the two subpopulations.

Table 5: ASAS20 Response Rates at Week 12 (ITT and Subpopulations NRI)

	ITT Population			Nr-axSpA (local lab)			AS (local lab)		
	PBO N=107	CZP200 N=111	CZP400 N=107	PBO N=50	CZP200 N=46	CZP400 N=51	PBO N=57	CZP200 N=65	CZP400 N=56
ASAS20 n(%)	41 (38%)	64 (58%)	68 (64%)	20 (40%)	27 (59%)	32 (63%)	21 (37%)	37 (57%)	36 (64%)
Difference vs PBO		19%	25%		19%	23%		20%	27%
95% CI		(6%, 32%)	(12%, 38%)		(-1%, 38%)	(4%, 42%)		(3%, 37%)	(10%, 45%)

Note: P-values based on Wald test & CIs based on normal approximation.

CZP=certolizumab; PBO=placebo; ITT=intent-to-treat; NRI=Non-responder imputation was applied to missing data; AS=ankylosing spondylitis; nr-axSpA=non-radiographic axial spondyloarthritis

Table 6: ASAS Components: Change from Baseline at Week 12 Analyses (ITT LOCF)

	ITT Population			nr-axSpA (local lab)			AS (local lab)		
	PBO N=107	CZP200 N=111	CZP400 N=107	PBO N=50	CZP200 N=46	CZP400 N=51	PBO N=57	CZP200 N=65	CZP400 N=56
Patient Global Disease Activity VAS (mm)	-1.19	-2.97	-3.13	-1.43	-3.19	-3.41	-1.26	-3.09	-2.98
Difference vs PBO		-1.6	-1.8		-1.8	-2.0		-1.5	-1.7
95% CI		(-2.3, -0.9)	(-2.5, -1.1)		(-2.9, -0.6)	(-3.1, -0.9)		(-2.4, -0.7)	(-2.6, -0.8)
Total Back Pain VAS	-1.40	-3.03	-2.91	-1.27	-3.50	-2.90	-1.51	-2.69	-2.91
Difference vs PBO		-1.7	-1.6		-2.3	-1.7		-1.4	-1.6
95% CI		(-2.3, -1.0)	(-2.2, -0.9)		(-3.2, -1.3)	(-2.7, -0.8)		(-2.2, -0.5)	(-2.5, -0.7)
Bath Ankylosing Spondylitis Functional Index	-0.56	-1.92	-2.01	-0.34	-2.07	-2.12	-0.75	-1.81	-1.90
Difference vs PBO		-1.5	-1.5		-1.8	-1.8		-1.2	-1.1
95% CI		(-2.0, -0.9)	(-2.0, -0.9)		(-2.7, -1.0)	(-2.6, -1.0)		(-1.9, -0.4)	(-1.9, -0.4)
Morning Stiffness (Mean of Q5 & Q6 on BASDAI Scale)	-1.22	-3.13	-3.16	-1.52	-3.77	-3.59	-1.17	-2.92	-3.01
Difference vs PBO		-1.9	-2.0		-2.2	-1.9		-1.8	-1.9
95% CI		(-2.6, -1.3)	(-2.6, -1.3)		(-3.2, -1.3)	(-3.0, -1.1)		(-2.6, -1.0)	(-2.8, -1.1)

Note: LS Means calculated from ANCOVA model with terms for treatment adjusting for region, prior anti-TNF α - exposure, and NY criteria for overall axSpA population), and baseline score as covariate.

CZP=certolizumab; PBO=placebo; ITT=intent-to-treat; LOCF=last observation prior to withdrawal or to missing measurement or before receiving CZP is carried forward; AS=ankylosing spondylitis; nr-axSpA=non-radiographic axial spondyloarthritis

Source: Adapted from Clinical Study Report PGADA-VAS Table 4.29.1 page 1664 and Table 4.29.2 page 1675; Total Back Pain Table 4.31.1 page 1752 and Table 4.31.2 page 1763; BASFI Table 4.14.1 page 1148, Table 4.14.2 page 1159 and Table 4.14.3 page 1170; Morning Stiffness Table 4.35.1 page 2045 and Table 4.34.2 page 2057

In this trial, patients were classified by the local lab readers into 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. Of the 147 nr-axSpA patients (local lab), only 69 patients (47%) were confirmed to be nr-axSpA by the central reader. Of the 178 AS patients (local lab), 112 patients (63%) were confirmed to be AS by the central reader. Note that 43 patients were not read centrally because of the delay from health authorities' approval of the amended protocol in some sites requiring central reading after study began with earlier protocol.

Table 7: Comparison of Investigator's and Central Reader's Sacroiliac X-ray Assessment

Investigator's Assessment at Screening	Central Reader Assessment at Baseline		Not-read centrally N=43
	mNY=NO (N=98) n (%)	mNY=YES (N=184) n (%)	
mNY=No (N=147)	69 (47)	72 (49)	6
mNY=YES (N=178)	29 (16)	112 (63)	37

CZP=certolizumab; PBO=placebo; AS=ankylosing spondylitis; nr-axSpA=non-radiographic axial spondyloarthritis; mNY=modified New York Criteria for AS; mNY=No implies nr-axSpA; mNY=Yes implies AS

In order to assess the impact of differences in classification between the local lab and central lab, additional subset analyses were performed. The subsets were formed by status of centrally-read x-ray images (i.e., negative or nr-axSpA and positive or AS, and non-centrally-read). The following analyses on the ASAS20 response endpoint were conducted by the reviewer:

1. Analyses based on each subset were conducted (i.e., centrally-read positive, centrally-read negative, and non-centrally-read) (Table 8).
2. Analyses on the new AS and nr-axSpA populations. The new nr-axSpA population was classified by taking a fraction of the 43 non-centrally-read patients similar to the prevalence of nr-axSpA centrally-read patients (i.e., 35%) and adding them to the centrally-read nr-ax-SpA (i.e., $98 + 15 = 113$). Similarly, the new AS population was classified by taking a fraction of the 43 non-centrally-read patients similar to the prevalence of AS centrally-read patients (i.e., 65%) and adding them to the centrally-read AS (i.e., $184 + 28 = 212$). Also the allocation of these new patients into CZP 200mg, CZP 400mg and placebo mimicked the actual randomization among the non-centrally-read patients. Then, the response rate for each treatment estimated from the non-centrally-read patients was assumed in imputing response for the corresponding treatment among the new patients (Table 9).
3. Analyses based on confirmed AS and confirmed nr-axSpA based on both local and central labs (Table 10).

Efficacy results favorable to CZP dose regimens were consistent on AS or nr-axSpA subgroups defined by modified NY criteria based on x-ray reading at central lab (Table 8). The magnitude of effect in ASAS20 response was slightly larger in the centrally-read nr-axSpA subgroup compared to the locally-read subgroup in both CZP arms (central-read: 22% and 26%,

respectively; locally read: 19% and 23%, respectively). The magnitude of effect in ASAS20 response was slightly smaller in the centrally-read AS subgroup compared to the locally read subgroup in both CZP arms (central-read: 15% and 23%, respectively; locally read: 20% and 27%, respectively).

Analysis on the new AS or the new nr-axSpA subpopulations also yielded positive results (Table 9). The magnitude of effect was consistent when compared to the results in Table 8.

Exploratory analyses were also conducted on subset of patients with confirmed central lab and local lab findings. These are the concordant pairs in Table 7. The sample sizes for each subpopulation were much smaller. However, the magnitude of effect in each subpopulation was still consistent.

Table 8: Primary Efficacy Results at Week 12 Based on Central X-ray Interpretation (Statistical Reviewer's ITT NRI Analyses)

	Centrally-Read						Not-centrally Read (N=43)		
	Nr-axSpA (N=98)			AS (N=184)			PBO N=15	CZP200 N=12	CZP400 N=16
	PBO N=35	CZP200 N=33	CZP400 N=30	PBO N=57	CZP200 N=66	CZP400 N=61			
ASAS20	7 (20%)	14 (42%)	14 (47%)	26 (46%)	40 (61%)	42 (69%)	8 (53%)	10 (83%)	12 (75%)
Difference vs PBO		22%	26%		15%	23%		30%	21%
95% CI		(1%, 44%)	(4%, 49%)		(-3%, 32%)	(6%, 41%)		(-3%, 63%)	(-11%, 55%)

Note: 95% CIs based on normal approximation (binary endpoints); CZP=certolizumab; PBO=placebo; ITT=Intent-to-treat; NRI=Non-responder imputation was applied to missing data (Binary Endpoint);

Table 9: Primary Efficacy Results at Week 12 Based on Central X-ray Interpretation (Statistical Reviewer's analysis with imputation)

	ITT Population (central lab)			Nr-axSpA (central lab)			AS (central lab)		
	PBO N=106	CZP200 N=113	CZP400 N=106	PBO N=39	CZP200 N=39	CZP400 N=35	PBO N=67	CZP200 N=74	CZP400 N=71
ASAS20 n(%)	41 (39%)	66 (58%)	66 (62%)	10 (26%)	19 (49%)	17 (49%)	31 (46%)	47 (64%)	49 (69%)
Difference vs PBO		20%	24%		23%	23%		17%	23%
95% CI		(7%, 33%)	(11%, 37%)		(2%, 44%)	(1%, 44%)		(1%, 33%)	(7%, 39%)

Note: 95% CIs based on normal approximation.

CZP=certolizumab; PBO=placebo; ITT=intent-to-treat; NRI=Non-responder imputation was applied to missing data; AS=ankylosing spondylitis; nr-axSpA=non-radiographic axial spondyloarthritis

Centrally not read subjects assigned to AS and nr-axSpA proportionally.

Table 10: Primary Efficacy Results at Week 12 Based on Both Local and Central X-ray Interpretation (Statistical Reviewer's Subgroup Analyses NRI)

	Both Local and Centrally-Read (Concordant Pairs)					
	Nr-axSpA			AS		
	PBO N=29	CZP200 N=23	CZP400 N=17	PBO N=38	CZP200 N=44	CZP400 N=30
ASAS20 n(%)	7 (24%)	11 (48%)	7 (41%)	14 (37%)	24 (55%)	19 (63%)
Difference vs PBO		24%	17%		18%	26%
95% CI		(-2%, 49%)	(-11%, 45%)		(-4%, 39%)	(3%, 50%)

Note: 95% CIs based on normal approximation (binary endpoints); CZP=certolizumab; PBO=placebo; ITT=Intent-to-treat; NRI=Non-responder imputation was applied to missing data (Binary Endpoint).

I was able to reproduce the applicant's results from the analyses of secondary endpoints with LOCF imputation strategy for missing values (Table 22 in Appendix). My summary on the secondary endpoints analyses with BOCF is consistent with the applicant's conclusion (Table 11, Table 12 and Table 13). Treatment differences in favor of CZP 200 mg and CZP 400 mg were significant for all four ranked secondary endpoints at Week 12 and at Week 24. A higher proportion of patients in the CZP 200 mg arm and in the CZP 400 mg achieved ASAS20 response and the change from baseline was greater in the CZP arms for BASFI, BASDAI, and BASMI compared to placebo at both weeks 12 and 24. There was no clear dose-response relationship between CZP 200 mg q2w and CZP 400 mg q4w. The data described here were based on local lab.

In addition to the four ranked secondary endpoints, analyses similar to the ASAS20 response were conducted to evaluate treatment difference in ASAS40 response. A larger treatment effect in ASAS40 response was observed compared to ASAS20 response in both dose groups when compared to placebo in the overall population and the subpopulations based on the local lab and for the nr-ax-SpA subpopulation based on the central lab (Table 14). Further, treatment differences were consistent in the overall population and across the AS and nr-axSpA subpopulations regardless of the lab where the x-ray images were read and regardless of the analyses conducted (Table 15 to Table 17).

Table 11: Secondary Endpoint: ASAS20 Response Rates at Week 24 (ITT and Subpopulations NRI)

	ITT Population			Nr-axSpA (local lab)			AS (local lab)		
	PBO N=107	CZP200 N=111	CZP400 N=107	PBO N=50	CZP200 N=46	CZP400 N=51	PBO N=57	CZP200 N=65	CZP400 N=56
ASAS20 at Week 24 n (%)	31 (29%)	74 (67%)	75 (70%)	12 (24%)	30 (65%)	36 (71%)	19 (33%)	44 (68%)	39 (70%)
Difference vs PBO		38%	41%		41%	47%		34%	36%
95% CI		(25%, 50%)	(29%, 53%)		(23%, 59%)	(29%, 64%)		(18%, 51%)	(19%, 54%)

Note: P-values based on Wald test & CIs based on normal approximation.

CZP=certolizumab; PBO=placebo; ITT=intent-to-treat; NRI=Non-responder imputation was applied to missing data; AS=ankylosing spondylitis; nr-axSpA=non-radiographic axial spondyloarthritis

Table 12: Secondary Efficacy Endpoints: Change from Baseline at Week 12 Analyses (ITT BOCF)

	ITT Population				Nr-axSpA (local lab)				AS (local lab)			
	PBO N=107	CZP200 N=111	CZP400 N=107	CZP200 +CZP400 N=218	PBO N=50	CZP200 N=46	CZP400 N=51	CZP200 +CZP400 N=97	PBO N=57	CZP200 N=65	CZP400 N=56	CZP200 +CZP400 N=121
BASFI Difference vs PBO	-0.61	-2.04	-1.99	-2.02	-0.54	-2.43	-2.28	-2.36	-0.63	-1.71	-1.69	-1.70
95% CI				-1.4 (-1.9, -0.9)				-1.8 (-2.5, -1.1)				-1.1 (-1.7, -0.4)
BASDAI Difference vs PBO	-1.26	-2.86	-2.80	-2.83	-1.47	-3.33	-3.34	-3.33	-1.14	-2.57	-2.45	-2.51
95% CI				-1.6 (-2.0, -1.1)				-1.9 (-2.6, -1.1)				-1.4 (-2.0, -0.8)
BASMI Difference vs PBO	-0.13	-0.60	-0.46	-0.5	-0.02	-0.61	-0.54	-0.58	-0.25	-0.57	-0.34	-0.46
95% CI				-0.4 (-0.6, -0.2)				-0.6 (-0.7, -0.3)				-0.2 (-1.5, -0.1)

Note: LS Means calculated from ANCOVA model with terms for treatment adjusting for region, prior anti-TNF α - exposure, and NY criteria for overall asSpA population), and baseline score as covariate.

CZP=certolizumab; PBO=placebo; ITT=intent-to-treat; BOCF=baseline value is carried forward to withdrawal or to missing measurement or before receiving CZP; AS=ankylosing spondylitis; nr-axSpA=non-radiographic axial spondyloarthritis

Table 13: Secondary Efficacy Endpoints: Change from Baseline at Week 24 Analyses (ITT BOCF)

	ITT Population				Nr-axSpA (local lab)				AS (local lab)			
	PBO N=107	CZP200 N=111	CZP400 N=107	CZP200 +CZP400 N=218	PBO N=50	CZP200 N=46	CZP400 N=51	CZP200 +CZP400 N=97	PBO N=57	CZP200 N=65	CZP400 N=56	CZP200 +CZP400 N=121
BASFI Difference vs PBO 95% CI	-0.77	-2.37	-2.30	-2.33 -1.6 (-2.0, -1.1)	-0.63	-2.42	-2.13	-2.28 -1.7 (-2.3, -1.0)	-0.89	-2.33	-2.39	-2.36 -1.5 (-2.1, -0.8)
BASDAI Difference vs PBO 95% CI	-1.06	-3.03	-3.07	-3.06 -2.0 (-2.5, -1.5)	-0.96	-3.09	-3.02	-3.05 -2.1 (-2.9, -1.3)	-1.14	-3.00	-3.14	-3.06 -1.9 (-2.5, -1.3)
BASMI Difference vs PBO 95% CI	-0.09	-0.57	-0.52	-0.55 -0.5 (-0.7, -0.3)	-0.06	-0.53	-0.48	-0.51 -0.6 (-0.9, -0.3)	-0.23	-0.61	-0.56	-0.58 -0.4 (-0.6, -0.1)

Note: LS Means calculated from ANCOVA model with terms for treatment adjusting for region, prior anti-TNF α - exposure, and NY criteria for overall asSpA population), and baseline score as covariate.

CZP=certolizumab; PBO=placebo; ITT=intent-to-treat; BOCF=baseline value is carried forward to withdrawal or to missing measurement or before receiving CZP; AS=ankylosing spondylitis; nr-axSpA=non-radiographic axial spondyloarthritis

Table 14: ASAS40 Response Rates at Week 12 (ITT and Subpopulations NRI)

	ITT Population			Nr-axSpA (local lab)			AS (local lab)		
	PBO N=107	CZP200 N=111	CZP400 N=107	PBO N=50	CZP200 N=46	CZP400 N=51	PBO N=57	CZP200 N=65	CZP400 N=56
ASAS40 n(%)	19 (18%)	48 (43%)	52 (49%)	8 (16%)	22 (48%)	24 (47%)	11 (19%)	26 (40%)	28 (50%)
Difference vs PBO		25%	31%		32%	31%		21%	31%
95% CI		(14%, 37%)	(19%, 43%)		(14%, 49%)	(14%, 48%)		(5%, 36%)	(14%, 47%)

Note: P-values based on Wald test & CIs based on normal approximation.

CZP=certolizumab; PBO=placebo; ITT=intent-to-treat; NRI=Non-responder imputation was applied to missing data; AS=ankylosing spondylitis; nr-axSpA=non-radiographic axial spondyloarthritis

Table 15: ASAS40 Response Rates at Week 12 Based on Central X-ray Interpretation (Statistical Reviewer's ITT NRI Analyses)

	Centrally-Read				Not-centrally Read (N=43)				
	Nr-axSpA (N=98)			PBO N=57	AS (N=184)		PBO N=15	CZP200 N=12	CZP400 N=16
	PBO N=35	CZP200 N=33	CZP400 N=30		CZP200 N=66	CZP400 N=61			
ASAS40 n(%)	4 (11%)	10 (30%)	11 (37%)	12 (21%)	32 (48%)	33 (54%)	3 (20%)	6 (50%)	8 (50%)
Difference vs PBO		19%	25%		27%	33%		30%	30%
95% CI		(-0%, 38%)	(5%, 45%)		(11%, 43%)	(17%, 49%)		(-5%, 65%)	(-2%, 62%)

Note: 95% CIs based on normal approximation (binary endpoints); CZP=certolizumab; PBO=placebo; ITT=Intent-to-treat; NRI=Non-responder imputation was applied to missing data (Binary Endpoint);

Table 16: ASAS40 Response Rates at Week 12 Based on Central X-ray Interpretation (Statistical Reviewer's analysis with imputation)

	Nr-axSpA			Centrally-Read		AS	
	PBO N=39	CZP200 N=39	CZP400 N=35	PBO N=67	CZP200 N=74	CZP400 N=71	
ASAS40 n(%)	5 (13%)	12 (31%)	14 (40%)	14 (21%)	36 (49%)	38 (54%)	
Difference vs PBO		18%	27%	14 (21%)	28%	33%	
95% CI		(0%, 36%)	(8%, 47%)		(13%, 43%)	(17%, 48%)	

Note: 95% CIs based on normal approximation (binary endpoints); CZP=certolizumab; PBO=placebo; ITT=Intent-to-treat; NRI=Non-responder imputation was applied to missing data (Binary Endpoint).

Centrally not read subjects assigned to AS and nr-axSpA proportionally.

Table 17: ASAS40 Response Rates at Week 12 Based on Both Local and Central X-ray Interpretation (Statistical Reviewer's Subgroup Analyses NRI)

	Both Local and Centrally-Read (Concordant Pairs)					
		Nr-axSpA			AS	
	PBO N=29	CZP200 N=23	CZP400 N=17	PBO N=38	CZP200 N=44	CZP400 N=30
ASAS40 n(%)	4 (14%)	9 (39%)	6 (35%)	8 (21%)	19 (43%)	16 (53%)
Difference vs PBO		25%	21%		22%	32%
95% CI		(2%, 49%)	(-5%, 47%)		(3%, 42%)	(10%, 54%)

Note: 95% CIs based on normal approximation (binary endpoints); CZP=certolizumab; PBO=placebo; ITT=Intent-to-treat; NRI=Non-responder imputation was applied to missing data (Binary Endpoint).

The following summarizes the current findings based on ASAS20 response.

1. All effects seen between CZP 200 mg and placebo are within the confidence interval.
 - a. Treatment difference based on local lab
 - i. Overall Population = 19% (6%, 32%)
 - ii. AS = 20% (3%, 37%)
 - iii. Nr-axSpA = 19% (-1%, 38%)
 - b. Treatment difference based on central lab
 - i. Overall Population = 20% (7%, 33%)
 - ii. AS = 17% (1%, 33%)
 - iii. Nr-axSpA = 23% (2%, 44%)

2. All effects seen between CZP 400 mg and placebo are within the confidence interval.
 - a. Treatment difference based on local lab
 - i. Overall Population = 25% (12%, 38%)
 - ii. AS = 27% (10%, 45%)
 - iii. Nr-axSpA = 23% (4%, 42%)
 - b. Treatment difference based on central lab
 - i. Overall Population = 24% (11%, 37%)
 - ii. AS = 23% (7%, 39%)
 - iii. Nr-axSpA = 23% (1%, 44%)

There is consistent evidence of a treatment effect in ASAS20 response between CZP 200 mg Q2W and placebo, and between CZP 400 mg Q4W and placebo in the overall population and across the subpopulations, regardless of whether they were read centrally or locally. The magnitude of effect for the AS population ranged from 17% to 20% between CZP 200 mg Q2W and placebo, and ranged from 23% to 27% between the CZP 400 mg Q4W and placebo. The magnitude of effect for the nr-axSpA population ranged from 19% to 23% between CZP 200 mg Q2W and placebo, and about 23% between the CZP 400 mg Q4W and placebo.

3.3 Evaluation of Safety

The assessment of the safety aspects of the study drug was mainly conducted by reviewing medical team, Drs Maynard and Yim.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In addition to the standard subgroup analyses based on patient demographics, I included subgroup analyses by region to see if there is any significant inconsistency of efficacy among regions and by baseline background treatment use.

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses were conducted by demographic variables of sex, age group, and race (Table 18). Each subgroup by demographics showed that there seems no noticeable interaction between treatment and demographic factors.

Table 18: Subgroup analyses by demographics

	N	n	ASAS20 Rate	Difference vs. PBO (95% CI)	p-value for interaction
Sex					0.22
Female					
PBO	42	15	36%		
CZP 200	44	18	41%	5% (-15%, 26%)	
CZP 400	39	22	57%	21% (-1%, 42%)	
Male					
PBO	65	26	40%		
CZP 200	67	46	69%	29% (12%, 45%)	
CZP 400	68	46	68%	28% (11%, 44%)	
Age					0.94
<45					
PBO	67	31	46%		
CZP 200	77	49	64%	17% (1%, 33%)	
CZP 400	67	47	70%	24% (8%, 40%)	
≥45					
PBO	40	10	25%		
CZP 200	34	15	44%	19% (-2%, 41%)	
CZP 400	40	21	53%	28% (7%, 48%)	
Race					0.31
White					
PBO	95	37	39%		
CZP 200	102	61	60%	21% (7%, 35%)	
CZP 400	96	60	63%	24% (10%, 37%)	
Non-White					
PBO	12	4	33%		
CZP 200	9	3	33%	0% (-41%, 41%)	
CZP 400	11	8	73%	40% (2%, 77%)	

Note: 95% CIs based on normal approximation. P-values for the interaction based on logistic regression with terms for treatment, the subgroup, and the subgroup-by-treatment interaction.

A subset analysis was conducted by geographic region to see if there was any noticeable difference in ASAS20 response rates between regions (EU and America). Each subgroup by region showed that there seems an effect favoring CZP over placebo in each region (Table 19).

Table 19: Subset analysis by study region (EU or America)

	N	n	ASAS20 Rate	Difference vs. PBO (95% CI)	p-value for interaction
Region					0.98
EU					
PBO	65	27	42%		
CZP 200	72	43	60%	18% (2%, 35%)	
CZP 400	67	44	66%	24% (8%, 41%)	
America					
PBO	42	14	33%		
CZP 200	39	21	54%	21% (-1%, 42%)	
CZP 400	40	24	60%	27% (6%, 47%)	

Note: 95% CIs based on normal approximation. P-values for the interaction based on logistic regression with terms for treatment, the subgroup, and the subgroup-by-treatment interaction.

4.2 Other Special/Subgroup Populations

The following analyses are the subgroup analyses by baseline characteristics, particularly, baseline CRP level, symptom duration, prior dmard use, and prior anti-TNF α use. CZP appears to be numerically better than placebo in each subset consistently in terms of ASAS20 response at Week 12 (Table 20).

Table 20: Subgroup analyses by baseline medical characteristics (ITT)

	N	n	ASAS20 Rate	Difference vs. PBO (95% CI)	p-value for interaction
CRP					0.43
≤15mg/L					
PBO	54	21	39 %		
CZP 200	69	36	52%	13% (-4%, 31%)	
CZP 400	69	44	64 %	25% (8%, 42%)	
≥15mg/L					
PBO	53	20	38 %		
CZP 200	42	28	67 %	29% (10%, 48%)	
CZP 400	38	24	63 %	25% (5%, 46%)	
Symptom Duration					0.98
<5 years					
PBO	42	16	38 %		
CZP 200	50	28	56 %	18% (-2%, 38%)	
CZP 400	34	21	62 %	24% (2%, 46%)	

≥5 years					
PBO	65	25	38 %		
CZP 200	61	36	59 %	21% (4%, 38%)	
CZP 400	73	47	64%	26% (10%, 42%)	
DMARD Use					0.33
Yes					
PBO	74	28	38 %		
CZP 200	66	41	62 %	24% (8%, 40%)	
CZP 400	65	39	60 %	22% (6%, 38%)	
No					
PBO	33	13	39 %		
CZP 200	45	23	51 %	12% (-10%, 34%)	
CZP 400	42	29	69 %	30% (8%, 51%)	
TNFα Use					0.56
Yes					
PBO	26	9	35%		
CZP 200	15	6	40%	5% (-25%, 36%)	
CZP 400	11	7	64%	29% (-5%, 63%)	
No					
PBO	81	31	40%		
CZP 200	96	58	61%	21% (7%, 35%)	
CZP 400	96	61	64%	24% (10%, 38%)	

Since some members of Advisory Committee recommended restricting the indicated population to patients with both positive MRI and elevated CRP, I conducted an analysis comparing ASAS20 response rates between treatments on this subgroup based on the local readings. Approximately 19% of 325 patients in the ITT set had both positive MRI and elevated CRP. Treatment difference in patients that are MRI positive and elevated CRP was about 21% and 11% for CZP 200 mg and CZP 400 mg, respectively, based on the local reading (Table 21).

Table 21: Subgroup Analysis by Inflammation Status

	N	n	ASAS20 Rate	Difference vs. PBO (95% CI)
Inflammation Status				
MRI+ & $\uparrow$CRP				
CZP 200	23	15	65 %	21% (-9%, 51%)
CZP 400	20	11	55 %	11% (-21%, 42%)
PBO	18	8	44 %	
Neither MRI+ nor $\uparrow$CRP				
CZP 200	88	49	56 %	19% (4%, 33%)
CZP 400	87	57	66 %	28% (14%, 43%)
PBO	89	33	37 %	

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

During the review of the clinical study, several statistical issues that warrant further exploration of data and discussion in the review were identified. The impact of missing data was not prominent because missing binary endpoints such as ASAS20 were treated conservatively using non-responder imputation. Missing continuous endpoints including ASAS20 components were imputed by the last observation carried forward (LOCF). Since only about 8 percent of all patients - 15 patients from CZP and 12 patients from placebo - withdrew during double-blind period, the concern on LOCF imputation on the analyses was not important. The proposed multiplicity adjustment method properly controlled type-1 error rate in the analyses of the secondary endpoints.

5.2 Comments on the proposed label

Following is an excerpt from the relevant clinical studies section in the proposed label. I generally agree with the study description. However, there are concerns about the presentation of efficacy results and they need to be discussed internally with the clinical team and the applicant. The following are general recommendations:

1. Removal of [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
2. Removal of [REDACTED] (b) (4)
[REDACTED] (b) (4)

[REDACTED] (b) (4)

5.3 Conclusions and Recommendations

In my opinion, the study provided a robust data supporting the efficacy of CZP meeting the pre-specified study success criterion: superiority of CZP to placebo in terms of ASAS20 response rate.

The major efficacy findings are as follows:

- A statistically significantly higher proportion of patients in the CZP 200 mg group had ASAS20 response at Week 12 compared to placebo.
- A statistically significantly higher proportion of patients in the CZP 400 mg group had ASAS20 response at Week 12 compared to placebo.
- A statistically significantly higher proportion of patients in the CZP 200 mg group had ASAS20 response at Week 24 compared to placebo.
- A statistically significantly higher proportion of patients in the CZP 400 mg group had ASAS20 response at Week 24 compared to placebo.
- A greater improvement from baseline in the BASFI in the CZP 200 mg + 400 mg group was achieved at Week 12 compared to the placebo group.
- A greater improvement from baseline in the BASDAI in the CZP 200 mg + 400 mg group was achieved at Week 12 compared to the placebo group.
- A greater improvement from baseline in the BASFI in the CZP 200 mg + 400 mg group was achieved at Week 24 compared to the placebo group.
- A greater improvement from baseline in the BASDAI in the CZP 200 mg + 400 mg group was achieved at Week 24 compared to the placebo group.
- A greater improvement from baseline in the BASMI in the CZP 200 mg + 400 mg group was achieved at Week 12 compared to the placebo group.
- A greater improvement from baseline in the BASMI in the CZP 200 mg + 400 mg group was achieved at Week 24 compared to the placebo group.

I conclude that the evidence of efficacy from the study is substantial and robust in terms of missing data handling though judged not important due to number of patients with missing data and in terms of subpopulations based on study region, baseline demographic and medical characteristics.

APPENDICES

Table 22: Applicant's Hierarchical Analysis of Significance Testing on Efficacy Endpoints

forward to Wee
^a Statistical signi
0.05 two-sided.
significant.
^b p-value was est
^c p-value was est
anti-TNF α exp

Source: Adapted from the clinical study report (page 139).

SIGNATURES/DISTRIBUTION LIST

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Date: September 5, 2013

Concurring Reviewer(s): Joan Buenconsejo, Ph.D.

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

/s/

YONGMAN KIM
09/09/2013

JOAN K BUENCONSEJO
09/09/2013
I concur.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125160Orig1s215

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

BLA	125160/215
Submission Date:	12/14/2012
Brand Name	Cimzia [®]
Submission Type	Efficacy Supplement
Generic Name	Certolizumab pegol (CZP)
OCP Reviewer	Liang Zhao, Ph.D.
Team Leader	Satjit Brar, Pharm.D., Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Pulmonary, Allergy and Rheumatology Products
Sponsor	UCB, Inc.
Formulation; Strength(s); Administration Route	Lyophilized powder and prefilled syringe; 200 mg; Subcutaneous injection
Approved 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
Approved Dosage Regimen	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
Proposed Indication	Treatment of adult patients with active axial spondyloarthritis (axSpA), including patients with ankylosing spondylitis (AS)
Proposed Dosage Regimen	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 or 400 mg every 4 weeks

1 Recommendation

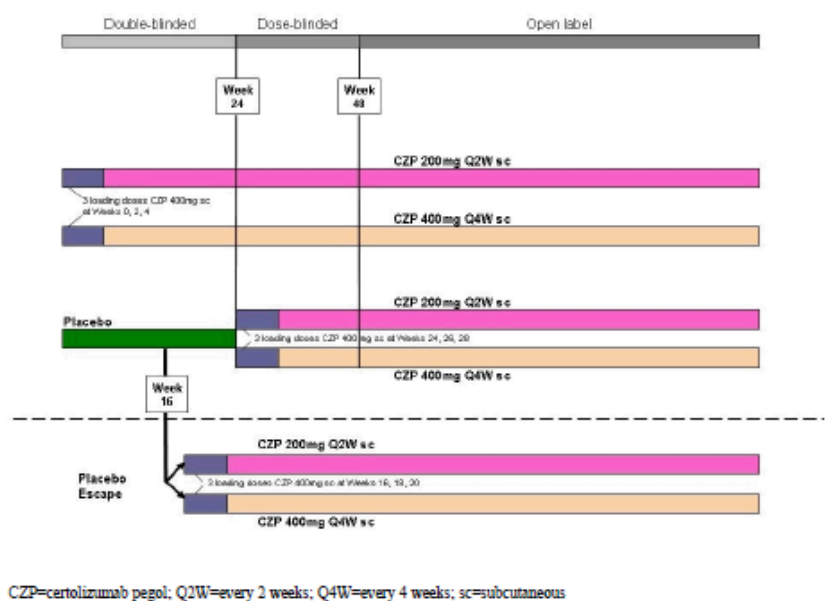
From a Clinical Pharmacology perspective, the application is acceptable.

2 Overall clinical pharmacology findings

The sponsor is applying for the approval of Cimzia for the axSpA indication, with the notion that treatment of axSpA, including AS and nr-axSpA, will be advanced by the addition of CZP to the physician's choices of approved medications.

This efficacy supplement is supported by a single Phase III (efficacy and safety) study AS001. This study was designed partially in accordance with meeting agreements between UCB and the FDA in 2009: 1) no additional dose-finding studies were required, and 2) the safety of CZP in AS001 is supported by the large rheumatoid arthritis (RA) safety database. Therefore, the doses selected for this study were based on the doses evaluated and shown to be safe and effective for the treatment of subjects with RA. AS001 is a multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study designed to evaluate the safety and efficacy of CZP in subjects with adult onset active axSpA (including AS). As shown in Figure 1, study AS001 included 5 study periods: Screening (up to 5 weeks), Double-blind Treatment Period (Week 0 to Week 24), Dose-Blind Treatment Period (Week 24 to Week 48), Open-Label Treatment Period (Week 48 to Week 158), and the Safety Follow-Up Period (Week 158 to Week 166). The clinical efficacy and safety data are reviewed by clinical reviewer Dr. Janet Maynard and statistical reviewer Dr. Yongman Kim. Refer to their reviews for details.

Figure 1 Study design of AS001



No clinical pharmacology studies have been included in the submission and no clinical pharmacology related label changes have been proposed by sponsor. In study AS001, no

additional clinical pharmacology information has been collected and there were too few antibody positive subjects to draw a meaningful conclusion regarding immunogenicity for the indication of axSpA.

2.1 Summary of the proposed label revisions related to clinical pharmacology

None.

3 Proposed label revisions

None.

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/s/

LIANG ZHAO
08/27/2013

SATJIT S BRAR
08/27/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125160Orig1s215

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: August 30, 2013

To: Nina Ton, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Adewale Adeleye, PharmD, MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, PharmD, Acting Team Leader, OPDP

Subject: BLA# 125160/S-215 - CIMZIA (certolizumab pegol) Lyophilized
powder or solution for subcutaneous use (Cimzia)

Reference is made to DPARP's consult request dated December 28, 2012, requesting review of the proposed Package Insert (PI), Carton and Container Labeling, and Medication Guide (MG) for Cimzia. The labeling has been updated as part of the above efficacy supplement for a new indication of ankylosing spondylitis. Reference is also made to the August 21, 2013, combined review from OPDP and DMPP regarding the Cimzia MG as part of S-213.

We refer to the e-mail from DPARP (Nina Ton) to OPDP (Adewale Adeleye) on August 14, 2013, indicating that there have been no changes to the Carton and Container Labeling with this supplement and that OPDP's review of the Carton and Container Labeling is not warranted at this time.

OPDP has reviewed the proposed PI and MG entitled, "BLA 125160 215 Cimzia Axial SpA label JM 08 16 13.doc" that was downloaded from the eroom using the link sent via e-mail from DPARP to OPDP on August 21, 2013. OPDP's comments on the PI and MG are provided directly on the attached copy of the labeling.

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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/s/

ADEWALE A ADELEYE
08/30/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Policy**

PATIENT LABELING REVIEW

Date: August 28, 2013

To: Badrul Chowdhury, 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)

Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling team
Division of Medical Policy Programs (DMPP)

From: Robin Duer, MBA, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): CIMZIA (certolizumab pegol)

Dosage Form and Route: lyophilized powder or solution for subcutaneous use

Application Type/Number: BLA 125160

Supplement number: 215

Applicant: UCB, Inc.

1 INTRODUCTION

On December 14, 2012, UCB, Inc. submitted for the Agency's review a Prior Approval supplemental New Biologics Application (BLA) for BLA 125160. The purpose of this submission is to provide for the addition of a new indication for the treatment of adults with active axial spondyloarthritis.

CIMZIA (certolizumab pegol) lyophilized powder or solution for subcutaneous use is a tumor necrosis factor (TNF) blocker originally approved on April 22, 2008 and 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

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology (DPARP) on December 28, 2012. DPARP requested that DMPP provide a focused review the Applicant's proposed Medication Guide (MG) for CIMZIA (certolizumab pegol) lyophilized powder or solution for subcutaneous use.

2 MATERIAL REVIEWED

- Draft CIMZIA (certolizumab pegol) lyophilized powder or solution for subcutaneous use Medication Guide (MG) received on December 14, 2012 and received by DMPP on December 28, 2012
- Draft CIMZIA (certolizumab pegol) lyophilized powder or solution for subcutaneous use Prescribing Information (PI) received on December 14, 2012, revised throughout the review cycle and received by DMPP on August 21, 2013
- DMPP and OPDP review of CIMZIA (certolizumab pegol) lyophilized powder or solution for subcutaneous use Medication Guide (MG) for S-213 dated August 21, 2013 and revised with DPARP on August 22, 2013

3 REVIEW METHODS

In 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- 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 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 on the correspondence.
- Our annotated version of the MG is appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

ROBIN E DUER
08/28/2013

MELISSA I HULETT
08/28/2013

LASHAWN M GRIFFITHS
08/28/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling, and Packaging Review

Date: June 17, 2013

Reviewer: Teresa McMillan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention & Analysis

Drug Name(s): Cimzia (Certolizumab Pegol)
For Injection

Strengths: 200 mg

Application Type/Number: BLA 125160

Submission Number: 213 and 215

Applicant/Sponsor: UCB, Inc.

OSE RCM #: 2012-2978 and 2013-77

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed insert labeling and medication guide for Cimzia (certolizumab pegol), BLA 125160 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Cimzia (certolizumab pegol) was approved 2008 for reducing the signs and symptoms of Crohn's disease and the treatment of adults with moderately to severely active rheumatoid arthritis. On November 28, 2012 and December 14, 2012 respectively, the Applicant submitted efficacy supplements for the proposed indication of active psoriatic arthritis and treatment of adult patients with active axial spondyloarthritis, including patients with ankylosing spondylitis.

1.2 PRODUCT INFORMATION

The following product information is provided in the November 28, 2012 and December 14, 2012 submissions.

- Active Ingredient: Certolizumab Pegol
- Indication of Use:
 - 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 patients with active psoriatic arthritis
 - Treatment of adult patients with active axial spondyloarthritis, including patients with ankylosing spondylitis
- Route of Administration: Subcutaneous
- Dosage Form: solution or powder for injection
- Strength: 200 mg
- Dose and Frequency:
 - Crohn's disease: 400 mg initially and then at weeks two and four, followed by every four weeks
 - Rheumatoid Arthritis: 400 mg initially and then at weeks two and four, followed by 200 mg every other week or 400 mg every four weeks
 - Psoriatic Arthritis: 400 mg (given as 2X 200 mg subcutaneous injections each) initially and at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks

- Axial Spondyloarthritis: 400 mg (given as 2X 200 mg subcutaneous injections each) initially and at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks
- How Supplied: Two configurations
 - Lyophilized powder for reconstitution (single use vial with 1 mL of sterile water for injection)
 - 200 mg/mL solution in a single-use prefilled syringe
- Storage: Refrigerate intact carton at 2 to 8 °C (36 to 46 °F)

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Cimzia medication error reports. We also reviewed the Cimzia package insert labeling and medication guide submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table.

Table 1: FAERS Search Strategy	
Date	Start date: 4/5/2012 (date of last AERS search in OSE Review# 2012-689) End date: 4/11/2013
Drug Names	(active ingredient) (active ingredient) (trade name) (verbatim term)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT Additional Terms as needed

The FAERS database search identified 29 cases. Each case was reviewed for relevancy and duplication. After individual review, 22 cases were not included in the final analysis for the following reasons:

- Adverse events not related to a medication error
- Accidental exposure- Cimzia listed as a concomitant medication
- Missed dose
- Intentional overdose
- No medication error reported

- Product quality issue-defective syringe -(narrative did not provide enough information to determine if a medication error occurred)

2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on April 11, 2013 for additional cases and actions concerning Cimzia. No additional cases were identified.

2.3 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Insert Labeling and Medication Guide submitted on November 7, 2012

2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Cimzia in OSE Label and Labeling Review #2012-686 and we looked at the reviews to ensure all our recommendation was implemented.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Cimzia labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, seven Cimzia medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter².

The remaining 7 medication errors are as follows:

- Wrong dose (n=4). Three of the wrong dose medication error cases involved patients receiving overdoses of 1200 mg every 4 weeks, 600 mg every 4 weeks, and 400 mg every 2 weeks. All doses were given for off labeled indications. No root cause or outcomes were reported.

The remaining case involved a patient who received 200 mg as an initial dose. No root cause or outcomes were reported.

- Wrong Frequency (n=3). In all cases, patients received their Cimzia dose at weekly or every 3 week intervals. No root cause or outcome was reported.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

We note that wrong frequency medication errors were noted in OSE Label and Labeling Review #2012-686. Analysis of the Cimzia Dosage and Administration Section determined that the dose and frequency of administration are clearly stated and are unlikely to be the cause of confusion resulting in the wrong dose and frequency of administration errors identified in the FAERS search. Additionally, none of the cases stated confusion resulting from the insert or instructions, therefore no changes are recommended at this time based on the identified cases.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

The Applicant is proposing two new indications of active Psoriatic Arthritis and Axial Spondyloarthritis. The proposed dose and frequency for both indications is 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks. The Applicant is proposing to use the currently approved 200 mg configurations. The currently approved formulation and strengths are adequate for use in administering the proposed dose of 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks. The medication guide and the insert labeling sufficiently reflects the proposed changes and no issues were identified.

4 CONCLUSIONS

DMEPA concludes that the proposed insert labeling and medication guide are acceptable and we have no further comments.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

TERESA S MCMILLAN
06/17/2013

LUBNA A MERCHANT
06/17/2013

Consultative Review and Evaluation of Clinical Data DPP Consult #11,374

Consultant Reviewer: Phillip D. Kronstein, M.D.
CDER/ODE-1/Division of Psychiatry Products

Consultation Requester: Nina Ton, RPM
Janet Maynard, M.D.
CDER/ODE-2/Division of Pulmonary, Allergy,
and Rheumatology Products

Subject: Humira (adalimumab; sBLA 125057/323)
Cimzia (certolizumab; sBLA 125160/215)

Date Received: April 4, 2013

Date Reviewed: April 22, 2013

I. Background

Adalimumab (Humira®) and certolizumab (Cimzia®) are recombinant human IgG1 monoclonal antibodies specific for human tumor necrosis factor (TNF) approved to treat a number of conditions. For adalimumab, this includes rheumatoid, juvenile idiopathic and psoriatic arthritis as well as ankylosing spondylitis, Crohn's disease, ulcerative colitis, and plaque psoriasis. For certolizumab, this includes Crohn's disease and rheumatoid arthritis. Efficacy supplements recently were submitted for adalimumab, for the treatment of non-radiographic axial spondylitis (sBLA 125057/323), as well as for certolizumab, for the treatment of axial spondyloarthritis (sBLA 125160/215). DPARP is taking both applications to an Advisory Committee, scheduled for July of this year, as these are novel indications that utilize new criteria for inflammatory back pain. During their review of the adalimumab efficacy supplement, DPARP noticed three cases of concern with regard to potential treatment-emergent suicidal behavior.

In sBLA 125057/323 (adalimumab), the primary safety data are from a single pivotal trial (M10-791), a 3-year study with a 12-week double-blind, placebo-controlled treatment period and a 144-week open label treatment period. The sponsor submitted data to Week 68. Of the 185 patients in this single pivotal trial, two died. One death was considered to be a suicide, while the cause of death for the second patient was unclear (suicide could not be ruled out). In addition, there was an SAE of a suicide attempt. Details of the cases are provided below.

- Subject (b) (6) was a 52-year-old white man with a relevant history of current heavy alcohol use (duration not provided) as well as anxiety, treated with sertraline (started almost two years before the study), who completed suicide by hanging on Day 223. Adalimumab was discontinued 40 days prior to the event due to lack of efficacy. An autopsy was not performed, and the death certificate was not obtained by the site.

- Subject (b) (6) was a 26-year-old white man with no known psychiatric history, other than past moderate drinking. He developed anxiety on Day 168, treated with PRN clonazepam (but was still ongoing), and insomnia on Day 466, treated with trazodone (resolved on Day 587), who died on Day 649, 14 days after the last dose of adalimumab. The subject, who was camping, was discovered unresponsive; he was pronounced dead at the scene. A companion reported that a “large” amount of alcohol was consumed the night prior to the subject’s death. The autopsy noted that the subject’s cause of death was cardiorespiratory failure due to opiate toxicity, including methadone and morphine (neither of which were on the subject’s medication list).
- Subject (b) (6) was a 23-year-old white man, with no known psychiatric history, with the adverse event of depression on Day 436, for which he received treatment (unclear with which drugs, as there are discrepancies in the narrative), who had a “suicide attempt” on Day 465. The subject reported “having suicidal ideation” one month prior to his suicide attempt, at the onset of his depression. He was distraught by job stress, family issues, his sibling’s diagnosis of multiple sclerosis, and relationship difficulties with his girlfriend. The subject overdosed on an unknown type and amount of soporifics and superficially cut his wrists. He received inpatient and outpatient treatment (including psychotherapy), and the event was considered resolved on Day 476. The adalimumab was not interrupted due to the event. According to the CRF, treatment continued every two weeks for another 12 weeks. The reason for discontinuation given at that point was that he felt he could not be compliant, due to a new job that involved overseas travel.

In the “Any Adalimumab” dataset, there were no adverse events leading to discontinuation listed under the “Psychiatric disorders” MedDRA System Organ Class. In terms of treatment-emergent adverse events during the double-blind treatment period, there were 2 subjects (2.8%) with the adverse event of “depression” in the adalimumab group vs. no subjects in the placebo group. We asked the sponsor for more information on these two subjects. They provided the following narratives:

- Subject (b) (6), a 36-year old male non-smoker, alcohol drinker (< 2 drinks per day), has had a history of depression and nervous breakdown since (b) (6). The subject was randomized into the adalimumab arm of the study in (b) (6). An adverse event of depression was reported with onset date of (b) (6) and treated with fluoxetine. The event was reported to be mild, non-serious, and not related to study drug by the investigator. The event was considered resolved on (b) (6).
- Subject (b) (6) a 21-year old male non-smoker and ex-drinker (previous history of more than 4 drinks per day), was initially reported as having an

adverse event of depression. However, after the database lock for the Week 68 cutoff, the site deleted this entry as the subject already had a prior diagnosis of depression. The subject's depressive episode was considered to be part of his ongoing disease. The investigator confirmed that this event was not considered to be a worsening of the pre-existing condition.

II. Response to DPARP Questions

- 1. Do the two patient deaths and one suicide attempt in study M10-791 raise concern regarding potential treatment-emergent suicidal ideation and behavior associated with adalimumab exposure? If so, could this be a concern with certolizumab, which has a similar mechanism of action and is proposed for use in a similar patient population?**

No, the two patient deaths and one suicide attempt in Study M10-791 do not raise concern regarding potential treatment-emergent suicidal ideation and behavior associated with adalimumab exposure. First, addressing each case individually:

- Subject (b) (6) had multiple risk factors for suicide, including ongoing heavy alcohol use and a long-standing anxiety disorder. He was suffering from axial spondylitis, which we understand is a chronic painful condition. Also, he had dropped out of the study due to lack of efficacy, which may have demoralized him further. Finally, it is important to note that he committed suicide a full 40 days after the last dose of adalimumab. For these reasons, his suicide was unlikely related to the study drug.
- Subject (b) (6) had an onset of depression and suicidal ideation while on adalimumab, but this was in the context of multiple job, family, and relationship stressors. It should be noted that, at the age of 23, this subject was within the peak age range for the onset of the first episode of depression. He was treated successfully while remaining on adalimumab for another 12 weeks. When he discontinued the drug, he was apparently doing well, as he had a new job that involved overseas travel. Therefore, his suicide attempt was unlikely related to the adalimumab.
- Subject (b) (6) died from an overdose of opiates and alcohol. He had developed anxiety while on study drug (treated with PRN clonazepam and was still ongoing at the time of the event), but the insomnia he had developed later had reportedly resolved. A companion on the camping trip implied that the subject had been drinking heavily the night before he was found dead, but there is no information about the subject's state of mind at the time. There is also no information about the opiates (morphine and methadone) found in his system. The subject had no known history of opiate abuse, but that does not

preclude the possibility, for instance, that his companion brought them on the camping trip for recreational use. So, the subject's death may have been an accidental overdose, but we cannot rule out suicide. If it was a suicide, we cannot rule out a relationship to study drug.

To summarize, out of the three cases, two (a completed suicide and a suicide attempt) are unlikely related to study drug. That leaves us with one case of accidental overdose vs. suicide, where if it was a suicide, we cannot rule out a relationship to study drug. One unclear case certainly does not constitute a signal of any kind. It is important to note that this death (actually all three cases) occurred during the open label phase of the trial, so there is no placebo arm for comparison. It is very possible that this study population, suffering from what is apparently a painful, chronic condition, may have a higher background rate of depression and suicide than the general population.

We are further reassured by the fact that in the "Any Adalimumab" dataset, there were no adverse events leading to discontinuation listed under the "Psychiatric disorders" MedDRA System Organ Class. For treatment-emergent adverse events during the double-blind treatment period, there were 2 subjects (2.8%) with the adverse event of "depression" in the adalimumab group vs. no subjects in the placebo group. However, review of the narratives provided by the sponsor (see above) showed that both subjects had a pre-existing history of depression, with one of the cases, after the database lock, no longer considered an adverse event.

2. Do you recommend additional analyses to assess for suicidal ideation and behavior, such as retrospective assessment with the Columbia classification criteria or review of post-marketing cases of suicide in the adalimumab program? If so, what analyses should be performed and should they also be performed with data from the certolizumab sBLA?

We do not recommend any additional analyses to assess for suicidal ideation and behavior, as we do not, after review of the available information for these cases, see a credible signal in Study M10-791 for treatment-emergent suicidal ideation and/or behavior associated with adalimumab. The possibility was raised of a search of the FAERS database for reports of depression and suicide/self-injury with adalimumab. However, this is not necessary and, if done, would likely not be informative. The reason is that the patient population for adalimumab, made up of individuals with chronic conditions that can be painful and/or debilitating (e.g. rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, or ulcerative colitis), likely has a higher background rate of depression and suicide than the general population.

Phillip D. Kronstein, M.D.
Medical Officer
CDER/DPP

cc: Kronstein
Khin
Mathis
Maynard (DPARP)
Yim (DPARP)
Ton (DPARP)

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/s/

PHILLIP D KRONSTEIN
05/09/2013

NI A KHIN
05/09/2013

MITCHELL V Mathis
05/09/2013

Division of Pulmonary, Allergy, and Rheumatology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: BLA 125160/215 Efficacy Supplement, Type SE1

Name of Drug: Cimzia (certolizumab pegol) Lyophilized Powder or Solution for Injection, 200 mg/mL

Applicant: UCB, Inc.

Labeling Reviewed

Submission Date: December 14, 2012

Receipt Date: December 17, 2012

Background and Summary Description:

This supplemental application proposes an indication for the treatment of adults with active axial spondyloarthritis. Cimzia was approved on April 22, 2008, for the treatment of adult patients with moderately to severely active Crohn's disease and on May 13, 2009, for moderately to severely active RA. The last approved labeling was on November 15, 2012. In this efficacy supplement, the sponsor submitted a package insert and a medication guide.

Review

Side-by-side comparison of the revised labeling submitted on March 8, 2013, to the last approved labeling for S-189 dated November 15, 2012, was conducted. The sponsor submitted the updated content of labeling March 8, 2013, based on the comments provided in the Filing Communication letter dated February 12, 2013. The labeling format issues identified in the Filing Communication letter were corrected. Below are the proposed revisions submitted by UCB, Inc.

Highlights Section (HL)

- The heading for the Boxed Warning has been changed from WARNING: RISK OF SERIOUS INFECTIONS to WARNING: SERIOUS INFECTIONS AND MALIGNANCY.
- The proposed additions to Indications and Usage, Dosage and Administration, Warnings and Precautions were listed under Recent Major Changes.
- The new indication [REDACTED] (b) (4) was added to Indications and Usage and Dosage and Administration sections.

Full Prescribing Information (FPI)

- The new indication (b) (4) was added to Section 1, Indications and Usage.
- The recommended dose of Cimzia (b) (4) was added to Section 2, Dosage and Administration.
- Subsection (b) (4) Concomitant Medications in Section 2, Dosage and Administration was updated with concomitant therapy used in (b) (4) clinical study.
- Cases of lymphoma in clinical trial patients were updated from three to (b) (4) in Subsection 5.2 Malignancies of Section 5, Warnings and Precautions. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL) in patients treated with TNF blockers were also added.
- Hypersensitivity reactions that may occur after the first administration of Cimzia was added in Subsection 5.4 of Section 5, Warnings and Precautions.
- The number of patients discontinued treatment, the most common adverse reactions for discontinuation of Cimzia, the number of patients in clinical trials exposed to Cimzia, the incidence rate of infections and most serious infections, and antibody formation in Subsection 6.1 Clinical Trials Experience, Section 6 Adverse Reactions were updated.
- Subsection (b) (4) which includes clinical data for the new indication was added to Section 14, Clinical Studies.

Recommendations

The proposed labeling changes are consistent with labeling changes submitted by the sponsor. Pending the review of this application by other disciplines, I recommend approval of the supplement.

Nina Ton	May 2, 2013
Regulatory Project Manager	Date
Ladan Jafari	May 2, 2013
Chief, Project Management Staff	Date

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PHUONG N TON
05/02/2013

LADAN JAFARI
05/02/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125160Orig1s215

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125160/200

MEETING MINUTES

UCB, Inc
900 Lake Drive
Georgia

Attention: Sandra Bonsall

Dear Ms. Bonsall:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Cimzia.

We also refer to the meeting between representatives of your firm and the FDA on July 31, 2012. The purpose of the meeting was 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.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, Regulatory Project Manager at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Philantha M. Bowen, M.P.H., RN
Senior Regulatory Project Management Officer
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

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MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: pre-sBLA

Meeting Date and Time: July 31, 2011; 1:30 – 3:00 PM
Meeting Location: WO 22, Conference Room

Application Number: 125160
Product Name: Cimzia®
Indication: Psoriatic Arthritis; Axial Spondyloarthritis
Sponsor/Applicant Name: UCB, Inc.

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder: Philantha Bowen, M.P.H., R.N.

FDA ATTENDEES

Office of Drug Evaluation II

Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of Pulmonary, Allergy, and Rheumatology Products

Lydia Gilbert-McClain, M.D., Deputy Division Director, Division of Pulmonary, Allergy, and Rheumatology Products

Philantha Bowen, M.P.H., RN, Senior Regulatory Management Officer, Division of Pulmonary and Allergy Products

Deborah Seibel, M.D., Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products

Banu Karimi-Shah, M.D., Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

Anthony Durmowicz, M.D., Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

Suzette Peng, M.D., Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products

Janet Maynard, M.D., Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products

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Office of Clinical Pharmacology

Liang Zhao, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II

Office of Translational Sciences

Joan Buenconsejo, Ph.D., Statistical Team Leader, Office of Biometrics, Division of Biometrics II

Kiya Hamilton, Ph.D., Statistical Reviewer, Office of Biometrics, Division of Biometrics II

Office of Surveillance and Epidemiology

Jane L. Gilbert, M.D., Ph.D., Medical Officer, Division of Pharmacovigilance II

Teresa McMillan, PharmD, Safety Evaluator, Division of Medication Errors and Prevention Analysis

SPONSOR ATTENDEES

Sandra Bonsall

Deborah Hogerman

Stefan Herdinius

Catherine Arendt MD

Christian Stach MD

Terri Arledge

Bengt Hoepken

Emmanuel Caeymax

Andreas Fichtner

Brenda van Lunen

Susan Williams MD

David Hebert PhD

Theresa Rosario-Jansen PhD

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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 (certolizumab pegol) is a humanized antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNF α), conjugated to polyethylene glycol. It is currently approved in the United States for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) and Crohn's disease (CD).

UCB submitted an End-of-Phase II meeting request dated March 6, 2009, to the Division of Analgesics and Anesthetic Products (DAAP), formally the Division of Analgesics, Anesthetics, and Rheumatology Products. This meeting request was denied, but DAAP agreed to provide responses to UCB's questions regarding their development program for psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA). In an advice letter dated February 9, 2010, DAAP provided written responses to the questions outlined in the meeting package dated June 2, 2009. In summary, the questions and responses centered on two trials: one for PsA and one for axSpA. DAAP concluded that it would be generally acceptable to use new ASAS classification criteria to select a broader population of subjects with axSpA, which would include early ankylosing spondylitis (AS).

UCB submitted a pre-sBLA meeting request to seek the following outcomes:

- Obtain FDA concurrence on the content and format of the two sBLA filings (PsA and axSpA).
- 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?

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FDA Response to Question 1: This approach is generally acceptable; however, support of the proposed indication will depend on the robustness of the data.

Discussion:

There was no discussion on question 1.

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 (b) (4) to support improvement of signs and symptoms. UCB plans to present the Baseline, Week 12, (b) (4) values 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.

Discussion:

There was no discussion on question 2.

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?

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.

Discussion:

For discussion on this subject matter, refer to the discussion section in question 5.

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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.

Discussion:

For discussion on this subject matter, refer to the discussion section in question 5.

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?

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FDA Response to Question 5: Refer to the response to Questions 3 and 4.

Discussion:

UCB requested that the Division provide additional clarification with respect to the concern with using extrapolated data when analyzing the mTSS, since the week 48 data would be the primary focus of a future submission. Before addressing UCB's request, the Division sought clarity on the number of proposed submissions for the indications. UCB clarified that they propose to submit three submissions which include two for PsA (first submission with data through week 24 and the second submission with data for mTSS at 48 weeks) and one for axSpA. For the week 24 and week 48 submissions in PsA, UCB is seeking signs and symptoms and inhibition of structural damage, respectively. UCB stated that the week 24 endpoint analysis for structural damage would be provided in the first submission for PsA. The Division recommended that UCB deliberate thoughtfully on the necessity of submitting the 24 and 48 week data as two separate supplements. Although the number of submissions is ultimately at UCB's discretion, the Division recommended the submission of one complete efficacy supplement for PsA.

With respect to the extrapolation of data for the mTSS, the Division expressed understanding that there were problems encountered with UCB's pre-specified imputation strategy for missing data. Due to these problems, UCB proposes to conduct sensitivity analyses that are not pre-specified. The Division explained that no specific comments could be conveyed about the proposed sensitivity analyses without reviewing the actual data. Since the data have already been unblinded, any results from the analyses of radiographic data will be a review issue.

UCB requested that the Division provide further clarification with respect to the concern with using observed data versus the randomized set for the analysis of the radiographic endpoint. The Division explained that the use of observed data is not recommended since excluding patients may introduce bias and influence the results. Furthermore, excluding patients from the analysis may not preserve the baseline comparability between treatment groups achieved by randomization.

The Division recommended that UCB evaluate the proportion of patients with no progression (i.e. responder analysis) as a sensitivity analysis. No progression (responder) is defined as change from baseline in mTSS ≤ 0 . The Division noted that by applying a responder analysis, missing data will not be an issue since patients who dropped out from the study or entered escape will be considered non-responders. In contrast, the analysis of mean change from baseline can be affected by extrapolated outliers that could potentially overestimate or underestimate treatment effects. Additionally, the Division stated that if the difference in proportion of patients with no progression is small, even though the treatment difference in mean change from baseline is statistically significant, this will certainly raise a concern and will be a review issue.

The Division referenced a recent advisory committee meeting and one of the key discussion points regarding the radiographic endpoint. The Division stated that there was general agreement among the committee members that it is harder to demonstrate treatment difference in

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radiographic outcomes given the complexity of the design of recent trials (i.e. short placebo-controlled period, cross-over by design, and missing data). The Division commented that in study PsA001, half of placebo subjects entered escape at week 16; therefore only half of placebo subjects have week 24 data. This implies that at week 48, placebo subjects will have 24 to 32 weeks of extrapolated data, thus making it difficult to make meaningful comparison between the active arms and placebo at Week 48.

The Division agreed that UCB's proposal to provide the results from the primary and sensitivity analyses in the submission was acceptable. The Division added that further analyses will be conducted during the review of the submission.

Finally, UCB asked if there was utility of their proposed plans for the week 48 submission. Currently, the data for week 48 is being compiled and is not unblinded. The Division responded that historically, long-term data for biologics was required. However, because we now have a better understanding of biologics therapies, we do not expect that a TNF blocker that inhibits structural damage early on would stop working at a later time point, i.e., data to support inhibition of structural damage at week 24 are unlikely to be contradicted by week 48 data. The proposed second submission at week 48 would provide primarily safety information. As a result, it is preferable that all data deemed necessary to support the application be in one submission.

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

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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.

Discussion:

UCB requested that the Division convey its rationale behind the change in viewpoint regarding the viability of axSpA as an indication on which drug approval could be based. The Division acknowledged the prior advice that UCB received from the Agency, and expressed understanding of the effect that changes in advice can have on a development program. However, the Division stated that as we have the opportunity to examine issues more closely, the possibility always exists that our thinking can evolve and change. Since the ultimate goal is to arrive at a development program that will be well-defined and beneficial to patients, a change in viewpoint is often necessary.

In considering UCB's program and other submissions with a proposed indication of axSpA, it has become apparent that the diagnostic ASAS criteria may be problematic in identifying an appropriate indication for drug approval. The ASAS criteria were developed for use in a clinical setting, with the goal of identifying patients more patients in the spectrum of inflammatory back pain, including patients with early AS. By design, these criteria were meant to be inclusive, as not to miss patients with the potential for developing progressive disease. As result, the ASAS criteria identify a heterogeneous group of patients. According to the ASAS criteria, patients with a positive HLA-B27, elevated CRP, and good response to NSAIDs would be labeled as having axial SpA, yet could have mechanical back pain, rather than inflammatory back pain. In addition, the prevalence and natural history of axial SpA is unclear. Previous literature suggests that up to half of patients with undifferentiated SpA have a self-limited illness with spontaneous remission after five years.

While these criteria may be appropriate for clinical use, they are problematic from a regulatory standpoint, as it is unclear whether the ASAS criteria identify a new and distinct disease that can form the basis of a new indication. Additional concerns include the potential transitory nature of the diagnoses, and the unclear progression and prevalence of disease. For example, while a certain percentage of patients identified by these criteria would develop AS, others may demonstrate non-progression or spontaneous resolution. Given these considerations, the Division informed UCB that is unclear at this point what an appropriate safety and efficacy profile would be to support drug approval for axSpA, even if one were to accept that this is a new disease entity. The Division further pointed out that axSpA is not an established diagnosis. Aside from two publications in 2009, in which a small number of professional groups supported acceptance of axSpA as a disease, it has not been prominent in the literature in the last four years. The Division advised UCB that it is impractical to try to define a disease and obtain approval for an indication at the same time. The Division commented that recognition of a

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disease can vary among regulatory agencies; the FDA has not always recognized diseases that are recognized by other countries.

Given the proposed broadening of the indication, and the larger number of patients that would be treated, the efficacy and safety data required to establish the risk:benefit profile for TNF blockers in axSpA is currently unclear. The Division informed UCB that this application could be submitted for review, but submission of the application should be carefully considered by UCB given the Division's underlying concerns. If submitted, given the novel regulatory issues, the efficacy supplement for axSpA would likely need to be discussed in a public forum, such as Advisory Committee, in order to seek guidance with respect to the risk-benefit profile of a TNF blocker in this setting. UCB informed the Division of their plan to submit the sBLAs by December 14, 2012, for PsA and December 20, 2012, for the axSpA.

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.

- ***Change from Baseline in ASAS core components at Weeks 12 (b) (4) to support improvement in signs and symptoms of axSpA.***
- ***Change from Baseline in the Bath Ankylosing Spondylitis Disease Functional Index (BASFI) at Weeks 12 (b) (4) to support improvement in physical function.***
- ***Change from Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI [total and component scores]) at Weeks 12 (b) (4) to support improvement in disease activity.***
- ***Change from Baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI linear) at Weeks 12 (b) (4) to support improvement in spinal mobility.***

(b) (4)

UCB understands that this is ultimately a review issue, and not all data are available at this time. However, does the Agency agree in principle that positive results will support presentation of these data in the Cimzia label?

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.

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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 the [REDACTED] (b) (4) you propose would be presented in the label, as there was no correction for multiplicity, and the validity of these instruments has not been established.

Discussion:

There was no discussion on question 7.

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.*

Discussion:

There was no discussion on question 8a.

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).***

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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.

Discussion:

There was no discussion on question 8b.

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.

Discussion:

There was no discussion on question 9a.

- 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?***

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- *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.*
- *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.

Discussion:

There was no discussion on question 9b.

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.

Discussion:

There was no discussion on question 10.

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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.*

Discussion:

There was no discussion on question 11.

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 UCB 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.*

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Discussion:

There was no discussion on question 12.

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.

Discussion:

There was no discussion on question 13.

3.0 GENERAL INFORMATION

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

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.

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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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

PHILANTHA M BOWEN
08/24/2012