

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**125160Orig1s213**

*Trade Name:* CIMZIA

*Generic or Proper Name:* certolizumab pegol

*Sponsor:* UCB, Inc.

*Approval Date:* September 27, 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.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 125160Origs213

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**125160Origs213**

**APPROVAL LETTER**



BLA 125160/213

**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 November 28, 2012, received November 29, 2012, submitted under section 351(a) of the Public Health Service Act for Cimzia (certolizumab pegol).

We acknowledge receipt of your amendments dated December 19, 2012, February 13, and 18, March 28, May 29, June 13, August 9, September 11, and 24, 2013.

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

**APPROVAL & LABELING**

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

**WAIVER OF HIGHLIGHTS SECTION**

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

**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(S):  
Content of Labeling

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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.**  
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/s/  
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SARAH K YIM  
09/27/2013  
Signing for Badrul Chowdhury, M.D., Ph.D.

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*APPLICATION NUMBER:*

**125160Origs213**

**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)

Lyophilized powder or solution 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.

### RECENT MAJOR CHANGES

Indications and Usage (1.3)	09/2013
Dosage and Administration (2.3, 2.7)	09/2013
Warnings and Precautions (5.2)	11/2012
Warnings and Precautions (5.5)	10/2012

### 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)

### 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.

### DOSAGE FORMS AND STRENGTHS

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

### CONTRAINDICATIONS

- None (4)

### WARNINGS AND PRECAUTIONS

- Serious infections – do not start CIMZIA during an active infection. If an infection develops, monitor carefully, and stop CIMZIA if infection becomes serious (5.1)
- 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](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2013

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**FULL PRESCRIBING INFORMATION: CONTENTS\***

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## 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).

## 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 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.

## **2.5 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.

## **2.6 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.

## **2.7 Concomitant Medications**

CIMZIA may be used as monotherapy or concomitantly with non-biological disease modifying anti-rheumatic drugs (DMARDs). In rheumatoid arthritis clinical studies, patients on CIMZIA therapy also took concomitant methotrexate (MTX) with the recommended CIMZIA dose of 200 mg every other week.

In the psoriatic arthritis clinical study, oral corticosteroids, DMARDs (methotrexate, leflunomide, sulfasalazine,) and NSAIDs were permitted as concomitant therapy.

CIMZIA should not be used in combination with biological DMARDs or other tumor necrosis factor (TNF) blocker therapy.

## **3 DOSAGE FORMS AND STRENGTHS**

### **• Lyophilized Powder for Reconstitution**

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

### **• Prefilled Syringe**

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

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.

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. 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.**

<b>Adverse Reaction (Preferred Term)</b>	<b>Placebo+ MTX<sup>#</sup> (%) N =324</b>	<b>CIMZIA 200 mg EOW + MTX(%) N =640</b>
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

<sup>#</sup>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.

#### 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**

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

### **7.3 Laboratory Tests**

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

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category B

#### 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 $\alpha$ , reproduction studies were performed in rats using a rodent anti-murine TNF $\alpha$  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 $\alpha$ , 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 overdose, 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 $\alpha$ ), 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 $\alpha$  with a KD of 90pM. TNF $\alpha$  is a key pro-inflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralizes TNF $\alpha$  (IC<sub>90</sub> of 4 ng/mL for inhibition of human TNF $\alpha$  in the *in vitro* L929 murine fibrosarcoma cytotoxicity assay) but does not neutralize lymphotoxin  $\alpha$  (TNF $\beta$ ). Certolizumab pegol cross-reacts poorly with TNF from rodents and rabbits, therefore *in vivo* efficacy was evaluated using animal models in which human TNF $\alpha$  was the physiologically active molecule.

Certolizumab pegol was shown to neutralize membrane-associated and soluble human TNF $\alpha$  in a dose-dependent manner. Incubation of monocytes with certolizumab pegol resulted in a dose-dependent inhibition of LPS-induced TNF $\alpha$  and IL-1 $\beta$  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 $\alpha$  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 $\alpha$  stimulates the production of downstream inflammatory mediators, including interleukin-1, prostaglandins, platelet activating factor, and nitric oxide. Elevated levels of

TNF $\alpha$  have been implicated in the pathology of Crohn's disease and rheumatoid arthritis. Certolizumab pegol binds to TNF $\alpha$ , inhibiting its role as a key mediator of inflammation. TNF $\alpha$  is strongly expressed in the bowel wall in areas involved by Crohn's disease and fecal concentrations of TNF $\alpha$  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 $\alpha$  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 $\alpha$ , reproduction studies were performed in rats using a rodent anti-murine TNF $\alpha$  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 (CDAI<sup>1</sup>) 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)
<b>Week 6</b>		
Clinical Response <sup>#</sup>	<b>27%</b> (22%, 32%)	<b>35%</b> (30%, 40%)*
Clinical Remission <sup>#</sup>	<b>17%</b> (13%, 22%)	<b>22%</b> (17%, 26%)
<b>Week 26</b>		
Clinical Response	<b>27%</b> (22%, 31%)	<b>37%</b> (32%, 42%)*
Clinical Remission	<b>18%</b> (14%, 22%)	<b>29%</b> (25%, 34%)*
<b>Both Weeks 6 &amp; 26</b>		
Clinical Response	<b>16%</b> (12%, 20%)	<b>23%</b> (18%, 28%)*
Clinical Remission	<b>10%</b> (7%, 13%)	<b>14%</b> (11%, 18%)
* p-value < 0.05 logistic regression test		
<sup>#</sup> 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
<b>Week 26</b>		
Clinical Response <sup>#</sup>	<b>36%</b> (30%, 43%)	<b>63%</b> (56%, 69%)*
Clinical Remission <sup>#</sup>	<b>29%</b> (22%, 35%)	<b>48%</b> (41%, 55%)*
* p < 0.05		
<sup>#</sup> 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<sup>(a)</sup> 200 mg + MTX q 2 weeks</u>  <u>N=393</u>	<u>CIMZIA<sup>(a)</sup> 200 mg + MTX - Placebo + MTX</u>  <u>(95% CI)<sup>(d)</sup></u>	<u>Placebo</u>  <u>N=109</u>	<u>CIMZIA<sup>(b)</sup> 400 mg q 4 weeks</u>  <u>N=111</u>	<u>CIMZIA<sup>(b)</sup> 400 mg - Placebo</u>  <u>(95% CI)<sup>(d)</sup></u>
<b>ACR20</b>						
Week 24	14%	59%	45% (38%, 52%)	9%	46%	36% (25%, 47%)
Week 52	13%	53%	40% (33%, 47%)	N/A	N/A	
<b>ACR50</b>						
Week 24	8%	37%	30% (24%, 36%)	4%	23%	19% (10%, 28%)
Week 52	8%	38%	30% (24%, 37%)	N/A	N/A	
<b>ACR70</b>						
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 <sup>(c)</sup>	1%	13%	12% (8%, 15%)	[Redacted]		

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

<sup>(b)</sup> CIMZIA administered every 4 weeks not preceded by a loading dose regimen

<sup>(c)</sup> Major clinical response is defined as achieving ACR70 response over a continuous 6-month period

<sup>(d)</sup> 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**

<b>Parameter<sup>†</sup></b>	<b>Study RA-I</b>				<b>Study RA-IV</b>			
	<b>Placebo + MTX N=199</b>		<b>CIMZIA<sup>(a)</sup> 200 mg + MTX q 2 weeks N=393</b>		<b>Placebo + MTX N=109</b>		<b>CIMZIA<sup>(b)</sup> 400 mg q 4 weeks Monotherapy N=111</b>	
	<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 <sup>(c)</sup>	66	56	65	25	4 (0.6)	3 (1.0)	4 (0.7)	3 (1.1)
Patient global assessment <sup>(c)</sup>	67	60	64	32	3 (0.8)	3 (1.0)	3 (0.8)	3 (1.0)
Pain <sup>(c)(d)</sup>	65	60	65	32	55 (20.8)	60 (26.7)	58 (21.9)	39 (29.6)
Disability index (HAQ) <sup>(e)</sup>	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

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

<sup>(b)</sup> CIMZIA administered every 4 weeks not preceded by a loading dose regimen

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

<sup>(d)</sup> Patient Assessment of Arthritis Pain. Visual Analog Scale: 0 = best, 100 = worst

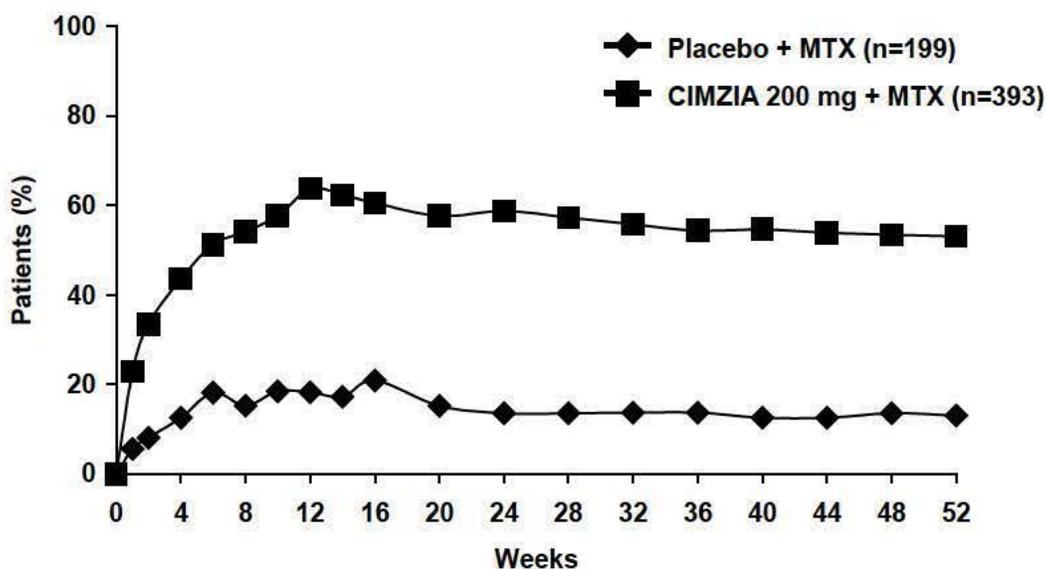
<sup>(e)</sup> Health Assessment Questionnaire Disability Index; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

All values are last observation carried forward.

<sup>†</sup>For Study RA-I, median is presented. For Study RA-IV, mean (SD) is presented except for CRP which presents geometric mean

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

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



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

### Radiographic Response

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

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

	<b>Placebo + MTX N=199 Mean (SD)</b>	<b>CIMZIA 200 mg + MTX N=393 Mean (SD)</b>	<b>CIMZIA 200 mg + MTX – Placebo + MTX Mean Difference</b>
<b>mTSS</b>			
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
<b>Erosion Score</b>			
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
<b>JSN Score</b>			
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  $\geq 3$  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 <sup>(c)</sup>	Placebo	CIMZIA <sup>(a)</sup> 200 mg Q2W	CIMZIA <sup>(b)</sup> 400 mg Q4W
	N=136	N=138	N=135
<b>ACR20</b>			
Week 12	24%	58%	52%
Week 24	24%	64%	56%
<b>ACR50</b>			
Week 12	11%	36%	33%
Week 24	13%*	44%	40%
<b>ACR70</b>			
Week 12	3%	25%	13%
Week 24	4%	28%	24%

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

<sup>(b)</sup> CIMZIA administered every 4 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4

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

<b>Patient global assessment<sup>(d, e)</sup></b>	57	50	60	33	60	40
<b>Pain<sup>(d, f)</sup></b>	60	50	60	33	61	39
<b>Disability index (HAQ)<sup>(d, g)</sup></b>	1.30	1.15	1.33	0.87	1.29	0.90
<b>CRP (mg/L)</b>	18.56	14.75	15.36	5.67	13.71	6.34

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

<sup>(b)</sup> CIMZIA administered every 4 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4

<sup>(c)</sup> Results are from the entire placebo group

<sup>(d)</sup> Last Observation Carried Forward is used for missing data, early withdrawals or placebo escape

<sup>(e)</sup> Patient and Physician Global Assessment of Disease Activity, VAS 0=best 100= worst

<sup>(f)</sup> The Patient Assessment of Arthritis Pain, VAS 0=no pain and 100= most severe pain

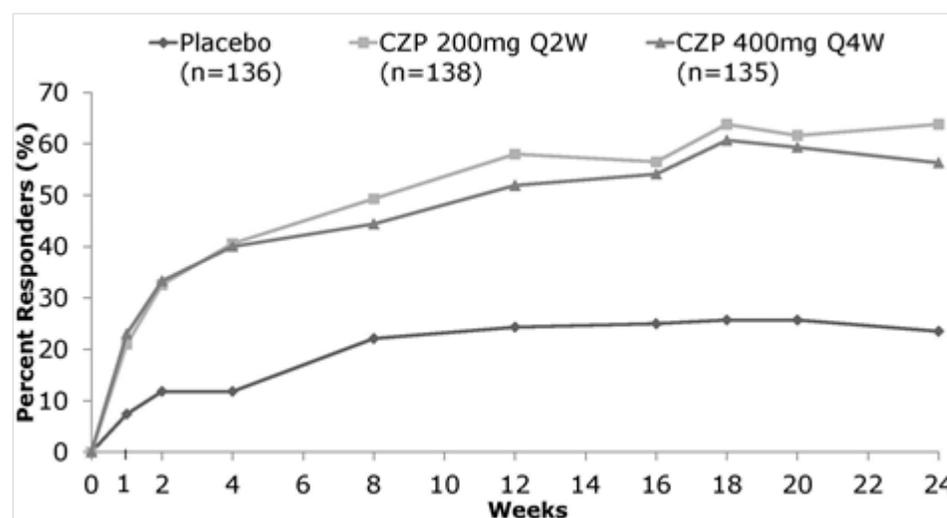
<sup>(g)</sup> The HAQ-DI, 4 point scale 0=without difficulty and 3=unable to do

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)).

## 15 REFERENCES

1. Best WR, Bechtel 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**

<u>Qty.</u>	<u>Item</u>
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

## **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<sup>®</sup> (anakinra), Orencia<sup>®</sup> (abatacept), Rituxan<sup>®</sup> (rituximab), or Tysabri<sup>®</sup> (natalizumab).
- medicines called Tumor Necrosis Factor (TNF) blockers such as Remicade<sup>®</sup> (infliximab), Humira<sup>®</sup> (adalimumab), Enbrel<sup>®</sup> (etanercept), or Simponi<sup>®</sup> (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 essentially free from particles. **Do not use the CIMZIA prefilled syringe if the medicine looks cloudy or if there are large or colored particles.**
- Do not miss any doses of CIMZIA. If you 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](http://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: 09/2013

**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

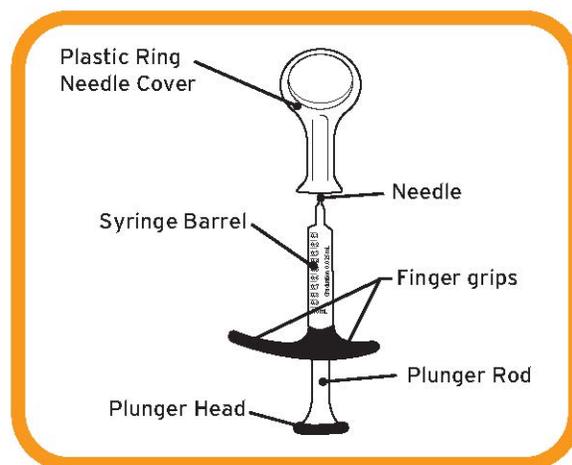


Figure B

## 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.

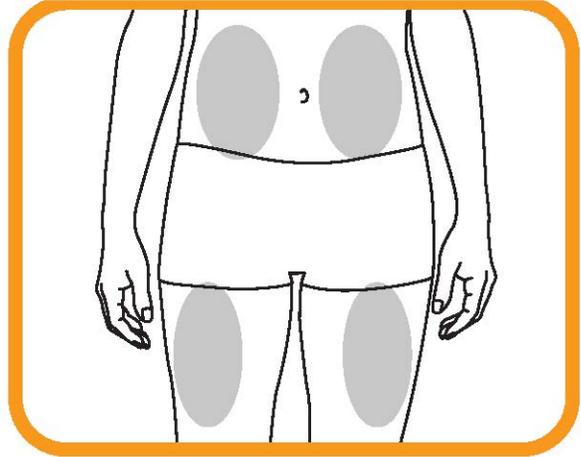


Figure D

### 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.

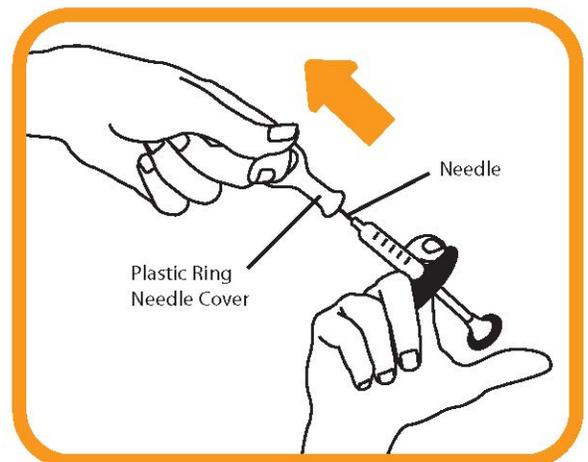


Figure E

**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.**

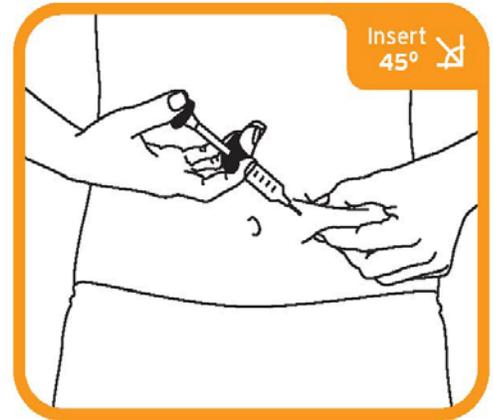


Figure G

**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 until the syringe is empty. **See Figure H.**

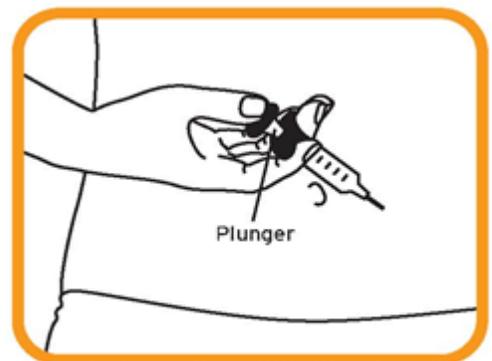


Figure H

**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**.

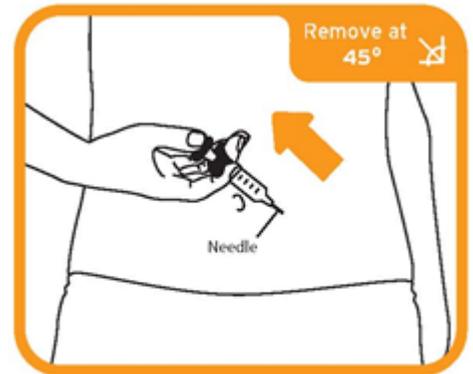


Figure I

**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.**

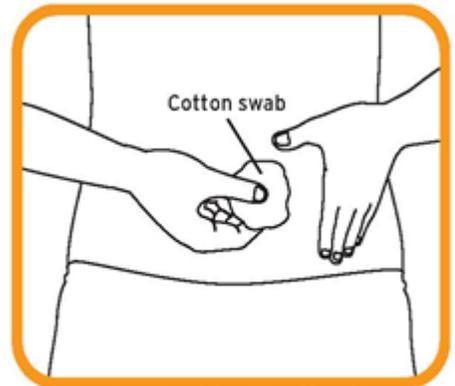


Figure J

**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 J**.

**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: 09/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125160Origs213**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Sarah Yim, M.D. Associate Director Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	125160
<b>Supplement #</b>	supplement 213
<b>Applicant Name</b>	UCB, Inc.
<b>Date of Submission</b>	November 29, 2012
<b>PDUFA Goal Date</b>	September 29, 2013
<b>Proprietary Name / Established (USAN) Name</b>	Cimzia® / certolizumab
<b>Dosage Forms / Strength</b>	200 mg lyophilized powder for reconstitution in single-use glass vial; 200 mg/mL solution in single-use prefilled syringe
<b>Proposed Indication(s)</b>	1. Active Psoriatic Arthritis
<b>Action:</b>	<i>Approval</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Suzette Peng, M.D.
Statistical Review	Kiya Hamilton, Ph.D.; Ruthanna Davi, Ph.D.
Pharmacology/Toxicology Review	No Pharmacology/Toxicology data submitted
CMC Review/OBP Review	No CMC data submitted
Microbiology Review	Not applicable
Clinical Pharmacology Review	No Clinical Pharmacology data submitted
OPDP	Adewale Adeleye, PharmD MBA; Kathleen Klemm PharmD
DSI	Not applicable
CDTL Review	Sarah Yim, M.D.
OSE/DMEPA	Teresa McMillan, PharmD; Lubna Merchant PharmD, M.S.; Scott Dallas, RPh
OMP/DMPP	Robin Duer, MBA BSN RN; Melissa Hulett RN BSN MBA; LaShawn Griffiths, MSHS-PH BSN RN

OND=Office of New Drugs  
 CMC=Chemistry, Manufacturing, and Controls  
 OBP=Office of Biotechnology Products  
 OPDP=Office of Prescription Drug Promotion  
 DSI=Division of Scientific Investigations  
 CDTL=Cross-Discipline Team Leader  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 OMP/DMPP=Office of Medical Policy, Division of Medical Policy Programs

## 1. Introduction

This is the supplemental biologic license application (sBLA) 125160, supplement 213, for Cimzia® (certolizumab) in Psoriatic Arthritis (PsA). Certolizumab is a pegylated anti-TNF $\alpha$  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. Certolizumab is available in a single-use vial (lyophilized powder for reconstitution, 200 mg) and prefilled syringe (PFS) of 200 mg/mL. A Risk Evaluation and Mitigation Strategy (REMS) was required to address the risks of serious infection (including tuberculosis and hepatitis B reactivation) and malignancy, as well as heart failure, neurologic reactions, hypersensitivity, cytopenias, and autoimmunity/lupus-like syndromes.

The sponsor's proposed indication is "treatment of adult patients with active psoriatic arthritis."

## 2. Background

PsA is an inflammatory arthritis, like rheumatoid arthritis (RA), however differs from RA in prevalence (lower, at 0.3 to 1% of the population), demographics (approximately equal male:female ratio, slightly younger mean age of late 40's), and joints involved (asymmetric, tendency toward distal involvement, involvement of the spine, and involvement of the tendons as well as synovium—dactylitis and enthesitis). In 80-85% of cases, skin involvement with psoriasis has occurred previously or contemporaneously with the joint disease. Because of its tendency to involve the spine (occurring in up to 40% of PsA patients) and lack rheumatoid factor (RF), PsA is considered one of the seronegative spondyloarthropathies. Approximately 20% of PsA patients develop a destructive, disabling arthritis, and approximately 50% of patients with early PsA have evidence of erosions.<sup>1</sup> Outcome measures utilized for RA, such as the American College of Rheumatology (ACR) response criteria and Health Assessment Questionnaire Disability Index (HAQ-DI, or HAQ) have been validated for use in PsA as well, have been used successfully in previous clinical trials of PsA, and were used in the certolizumab PsA trial.

Thus far, four TNF inhibitors, have been approved for PsA: Enbrel® (etanercept) on January 15, 2002, Remicade® (infliximab) on 5/18/2005, Humira® (adalimumab) on October 3, 2005, and Simponi® (golimumab) on April 24, 2009. The IL12/23-blocking monoclonal antibody

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<sup>1</sup> Gladman DD, et al., "Psoriatic arthritis: epidemiology, clinical features, course, and outcome." *Annals of Rheumatic Disease*, 2005, 64:14-17.

Stelara® (ustekinumab) was approved for PsA on September 20, 2013. Upon approval, certolizumab would be the fifth TNF inhibitor and sixth biologic product approved for PsA.

### *Regulatory History*

IND 9869 was originally opened on June 8, 2001 for the Crohn's disease indication. In September 2005, with the reassignment of products from the CBER Division of Therapeutic Biologic Medicine Products to the CDER review divisions, the Crohn's disease protocols were consolidated under IND 11197, overseen by the Division of Gastroenterology Products (DGP) and the rheumatic disease protocols remained under IND 9869, overseen by the then Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP). The applicant submitted an End-of-Phase 2 (EOP2) meeting request for the PsA and Axial Spondyloarthritis (AxSpA) indications in March 2009. This meeting request was denied but written responses were provided to the sponsor after consultation was obtained from the Study Endpoints and Labeling Development (SEALD) team regarding the proposed use of patient-reported outcome (PROs) measures in the proposed trials. This feedback was provided in February 2010.

At that time DAARP generally agreed with the proposed trial design in PsA (primary endpoints of American College of Rheumatology 20% improvement response criteria (ACR20) at Week 12 and modified Total Sharp Score (mTSS) at Week 24. The sponsor proposed an initial supplemental application that would include ACR20 and health assessment questionnaire-disability index (HAQ-DI) results and a second application with radiographic outcome results and more extended duration (Week 48) ACR20 and HAQ-DI results. DAARP relayed SEALD comments regarding the (b) (4)

At the pre-sBLA meeting for the PsA and AxSpA indications on July 31, 2012, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) agreed that the PsA trial and endpoints appeared to be generally reasonable. Additional detailed discussion took place regarding the analysis of the radiographic endpoint and approaches to handling missing data and extrapolating placebo data for the Week 48 timepoint. Based on their review of the radiographic data, the sponsor proposed to provide post-hoc analyses using an 8 week minimum time interval between radiographs and other imputation methods that were not pre-specified. UCB was allowed to submit all analyses and this would be a review issue.

## **3. CMC/Device**

No CMC/Device data were submitted with this supplemental BLA. No changes to the marketed product presentation, manufacturing, or controls for certolizumab were proposed in this submission. There are no outstanding issues.

## **4. Nonclinical Pharmacology/Toxicology**

No nonclinical studies were submitted with this sBLA. There are no outstanding issues.

## **5. Clinical Pharmacology/Biopharmaceutics**

No clinical pharmacology data were submitted in this sBLA. There are no outstanding issues.

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical-Efficacy**

A single multicenter randomized double-blind placebo-controlled study in 393 PsA patients was conducted (Study PsA001). The study was designed with a 24-week controlled period, where patients received certolizumab 400 mg subcutaneously (sc) at Weeks 0, 2 and 4, followed by 200 mg sc every 2 weeks (200 mg q2w) or 400 mg every 4 weeks (400 mg q4w) or placebo. The doses selected for study in PsA were based on the doses evaluated and shown to be safe and effective for the treatment of patients with RA.

The primary efficacy endpoint in PsA001 was the proportion of ACR20 responders at Week 12. The ACR20, ACR50, and ACR70 is defined as a 20%, 50% or 70% improvement, respectively, from baseline in tender joint count and swollen joint count, and the same level of improvement in at least 3 of the 5 following variables: patient pain on a visual analog scale (VAS), patient global assessment of disease activity on a VAS, physician global assessment of disease activity on a VAS, Health Assessment Questionnaire-Disability Index (HAQ-DI), and C-reactive protein (CRP).

The primary efficacy analysis utilized a non-responder for missing data. Twenty-four percent of placebo-treated patients experienced an ACR20 response at Week 12, compared to 58% of patients in the certolizumab 200 mg q2w group and 52% of patients in the certolizumab 400 mg q4w group. Thus both certolizumab dose regimens resulted in approximately 30% more ACR20 responders compared to placebo, and this difference is statistically significant. The efficacy of certolizumab for clinical responses was corroborated by similarly positive and statistically significant treatment effects on ACR50 and ACR70 responses, HAQ-DI change from baseline, proportion of patients with a HAQ-DI improvement of at least 0.3 units, and the proportion of patients (with at least 3% body surface area involved by psoriasis) who achieved an at least 75% improvement in Psoriasis Area and Severity Index (PASI75).

The applicant identified the radiographic endpoint, change from baseline to Week 24 in the modified Total Sharp Score (mTSS), as the second major efficacy objective of the trial. The mTSS is a radiographic scoring system that quantifies the extent of bone erosions and joint

space narrowing (JSN) for 64 and 52 joints, respectively, with higher scores representing greater damage. The maximum possible scores were 320 for erosions, 208 for JSN, and 528 for the total score. However, patients' scores are typically much lower, because only a fraction of all the possible joints are involved at any given time.

In the applicant's pre-specified analysis, scores for patients who withdrew for any reason, or patients with missing Week 24 measurement, or placebo patients who used rescue medication were linearly extrapolated from the last two radiographs before Week 24 or the early withdrawal or before receiving rescue medication. Missing baseline mTSS measurements were imputed with the minimum value observed, which was 0. If a patient was missing at least two measurements including Week 24, then the missing Week 24 score was imputed with the maximum value observed in this study, which was 356.6. This value was observed in a single patient who was in the CZP 400 mg q4w group. Although linear extrapolation has been used in previous clinical development programs for PsA, the other aspects of this pre-specified analysis plan were unique and led to primary analysis results which were greatly skewed due to the imputation of the maximum value for missing data throughout the groups.

FDA statistical reviewers noted that many of the patients with less than 2 mTSS observations were being counted in this category because they had escaped to rescue medication. Thus they performed an analysis where patients who had escaped were included in the analysis using their observed values, even though these values occurred while the patient was on rescue medication. For patients who had mTSS scores from two time points before Week 24, linear extrapolation was used to impute an mTSS score at Week 24. Patients who did not have at least 2 available x-rays were excluded from the analysis. This analysis was considered to provide a conservative estimate of the treatment difference because of the likelihood that escaped placebo patients would be expected to have better scores on rescue treatment.

As summarized in Table 1 below, using FDA's analysis, certolizumab 200 mg q2w was associated with a statistically significant reduction in structural damage progression as assessed by mTSS compared to placebo add-on treatment. Results for the 400 mg q4w arm trended in the right direction but were not significantly different from placebo.

**Table 1: FDA Analysis of Radiographic Endpoint: Change from Baseline in mTSS at Week 24**

	Placebo Total N = 136	CZP 200 mg q2w Total N = 138	CZP 400 mg q4w Total N = 135	CZP Combined Total N = 273
<b>FDA Analysis: Exclusion of patients with &lt; 2 available x-rays; inclusion of escape patient observed data</b>				
Sample Size	n = 123*	n = 130	n = 123	n = 253
Mean change from baseline in mTSS	0.18	-0.02	0.09	0.03
Difference between vs. pbo (p-value)		-0.21 (p = 0.017)	-0.10 (p = 0.261)	-0.15 (p = 0.042)

\*For patients escaping from placebo to CZP, their observed data on CZP are utilized for calculation  
Source: Table 11 from Dr. Hamilton's statistical review

### *Efficacy Conclusions*

The clinical and statistical teams are in agreement that Study PsA001 provides substantial evidence of the efficacy of certolizumab for treatment of active psoriatic arthritis, based on multiple measures of clinical response, including the primary efficacy endpoint of the proportion of ACR 20 responders at Week 12. Although the applicant's pre-specified analysis

for the radiographic endpoint yielded unusual results due to a single outlier, FDA's analyses of the radiographic results using conservative missing data handling methods supported a conclusion of a beneficial treatment effect associated with CZP. The difference compared to placebo was only statistically significant with the CZP 200 mg q2w dose regimen, although the trend for the CZP 400 mg q4w dose regimen was also consistent with a favorable treatment effect.

## 8. Safety

- *Major safety concerns related to labeling*

Like other TNF inhibitors, the currently approved certolizumab label contains a boxed warning regarding an increased risk for serious infections (including tuberculosis, invasive fungal, and opportunistic infections) and the observation of lymphoma and other malignancies in children and adolescents treated with TNF inhibitors. Also consistent with other TNF inhibitors, the Warnings and Precautions section of the label includes serious infections, malignancy, heart failure, hypersensitivity reactions, hepatitis B virus reactivation, neurologic reactions, cytopenias, autoimmunity/lupus-like syndrome, and to avoid live vaccines during treatment. No unique safety signals have been identified for certolizumab apart from the expected concerns observed with TNF inhibitors.

The certolizumab PsA safety database was limited to 24-week results from study PsA001. Through the data cutoff date of 31 May 2013, 358 patients received at least 6 months of certolizumab and 279 patients received at least 12 months of certolizumab. Overall, the incidence and types of death and nonfatal serious adverse events observed appeared to be consistent with the clinical development program of certolizumab in RA and other TNF inhibitors. No new safety signals were identified.

- *Postmarketing data*

The bulk of the safety experience with certolizumab has been in the approved indications of Crohn's disease and RA. This experience was evaluated via mandated postmarketing safety assessments as part of the REMS and as part of Section 915 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). The safety profile of certolizumab has been consistent with the safety profile of other TNF inhibitors.

- *Final labeling recommendations*

No major safety-related changes are warranted on the basis of this submission. The basic safety information from study PsA001 will be included in Section 6.1 of the prescribing information.

- *REMS*

While certolizumab previously had a medication guide-only REMS, and a REMS modification to include a communication plan regarding the risk of invasive fungal infections (applicable to all TNF inhibitors), the REMS requirement was released on July 26, 2011. At present, certolizumab continues to have a medication guide to communicate the risks of serious infections, including tuberculosis, invasive fungal infections, and hepatitis B reactivation, and the risk of malignancy, consistent with other approved TNF inhibitors.

- *PMRs and PMCs*

No postmarketing requirements or postmarketing commitments are warranted on the basis of the safety data in this submission.

## 9. Advisory Committee Meeting

No issues were identified to warrant an advisory committee meeting for this efficacy supplement.

## 10. Pediatrics

The applicant requested, and was granted, a full waiver from the Pediatric Research Equity Act (PREA) requirements for the reason that studies are impossible or highly impractical. This is because the subset of children who would develop psoriatic arthritis is difficult to specifically diagnose among patients with juvenile idiopathic arthritis. This was discussed at the Pediatric Review Committee (PeRC) meeting on August 14, 2013, and PeRC was in agreement with granting the waiver. A pediatric study in polyarticular juvenile idiopathic arthritis patients ages 2 to 17 is a postmarketing requirement associated with the approval of certolizumab for RA, and is ongoing.

## 11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

## 12. Labeling

- *Proprietary name*—approved as Cimzia.
- *Physician labeling (major issues that were discussed, resolved, or not resolved)*

The applicant agreed to use Dosage and Administration language for PsA that is the same as for RA. Specifically, after the 400 mg loading dose, 200 mg every 2 weeks will be the default maintenance dose, and 400 mg every 4 weeks can be considered. The applicant proposed to mention that certolizumab improved skin manifestations in patients with PsA but also state that the safety and efficacy of Cimzia in the treatment of patients with plaque psoriasis has not been established. The review team agreed this was reasonable. The applicant also agreed to

include radiographic results based on FDA's preferred analysis using observed data for placebo-patients who crossed over to rescue treatment. The Study Endpoints and Labeling Development (SEALD) team identified outstanding labeling format deficiencies which were corrected by the applicant. Some additional non-required format and content recommendations were made by SEALD which will not be addressed with this efficacy supplement as there is insufficient time remaining in the review cycle and these recommendations will need to be discussed with the home division for this product, the Division of Gastrointestinal and Inborn Error Products (DGIEP).

- *Carton and immediate container labels*—No proposed changes or issues.
- *Patient labeling/Medication guide*—Minor changes were proposed by the applicant to accommodate the new indication.

### **13. Decision/Action/Risk Benefit Assessment**

- **Regulatory Action**

The action on this efficacy supplement will be approval.

- **Risk Benefit Assessment**

The review team is in agreement that risk-benefit profile of certolizumab is favorable for the treatment of active psoriatic arthritis in adults. Substantial evidence was provided that certolizumab treatment was associated with improvement in clinical responses, as captured by ACR response criteria, HAQ-DI, and PASI 75, as well as reduction in structural damage, as captured by the change from baseline to Week 24 in mTSS. The safety profile of certolizumab in PsA was consistent with the known safety profile of certolizumab as established in the approved indications of RA and Crohn's Disease, and also with the safety profile of other TNF inhibitors.

- **Postmarketing Risk Evaluation and Mitigation Strategies (REMS)**

As described in Section 8, the REMS requirement for certolizumab was released on July 26, 2011. At present, certolizumab continues to have a medication guide to communicate the risks of serious infections, including tuberculosis, invasive fungal infections, and hepatitis B reactivation, and the risk of malignancy. No changes to the current status are warranted on the basis of the information in this submission.

- **Other Postmarketing Requirements and Commitments**

No postmarketing requirements or commitments are warranted.

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/s/  
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SARAH K YIM  
09/26/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125160Origs213**

**OFFICER/EMPLOYEE LIST**

**Officer/Employee List**  
**sBLA 125160/213 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

Davi, Ruthanna C

Duer, Robin

Hamilton, Kiya

Hulett, Melissa

Ladan Jafari

Maynard, Janet

Merchant, Lubna

Muthukkumar, Subramanian

Nikolov, Nikolay

Peng, Suzette

Ton, Nina

Yim, Sarah

Zhao, Liang

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125160Origs213**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	September 8, 2013
<b>From</b>	Sarah Yim, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	125160
<b>Supplement#</b>	supplement 213
<b>Applicant</b>	UCB, Inc.
<b>Date of Submission</b>	November 29, 2012
<b>PDUFA Goal Date</b>	September 29, 2013
<b>Proprietary Name / Established (USAN) names</b>	Cimzia® / certolizumab
<b>Dosage forms / Strength</b>	200 mg lyophilized powder for reconstitution in single-use glass vial; 200 mg/mL solution in single-use prefilled syringe
<b>Proposed Indication(s)</b>	1. Active Psoriatic Arthritis
<b>Recommended:</b>	<i>Approval</i>

### 1. Introduction

This is the supplemental biologic license application (sBLA) 125160, supplement 213, for Cimzia® (certolizumab) in Psoriatic Arthritis (PsA). Certolizumab is a pegylated anti-TNF $\alpha$  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. Certolizumab is available in a single-use vial (lyophilized powder for reconstitution, 200 mg) and prefilled syringe (PFS) of 200 mg/mL. A Risk Evaluation and Mitigation Strategy (REMS) was required to address the risks of serious infection (including tuberculosis and hepatitis B reactivation) and malignancy, as well as heart failure, neurologic reactions, hypersensitivity, cytopenias, and autoimmunity/lupus-like syndromes.

The sponsor's proposed indication is "treatment of adult patients with active psoriatic arthritis."

### 2. Background

PsA is an inflammatory arthritis, like rheumatoid arthritis (RA), however differs from RA in prevalence (lower, at 0.3 to 1% of the population), demographics (approximately equal male:female ratio, slightly younger mean age of late 40's), and joints involved (asymmetric, tendency toward distal involvement, involvement of the spine, and involvement of the tendons as well as synovium—dactylitis and enthesitis). In 80-85% of cases, skin involvement with psoriasis has occurred previously or contemporaneously with the joint disease. Because of its tendency to involve the spine (occurring in up to 40% of PsA patients) and lack rheumatoid factor (RF), PsA is considered one of the seronegative spondyloarthropathies. Approximately 20% of PsA patients develop a destructive, disabling arthritis, and approximately 50% of patients with early PsA have evidence of erosions.<sup>1</sup> Outcome measures utilized for RA, such as the American College of Rheumatology (ACR) response criteria and Health Assessment Questionnaire Disability Index (HAQ-DI, or HAQ) have been validated for use in PsA as well, have been used successfully in previous clinical trials of PsA, and were used in the certolizumab PsA trial.

Thus far, four biologics, all TNF inhibitors, have been approved for PsA: Enbrel® (etanercept) on January 15, 2002, Remicade® (infliximab) on 5/18/2005, Humira® (adalimumab) on October 3, 2005, and Simponi® (golimumab) on April 24, 2009.

### *Regulatory History*

IND 9869 was originally opened on June 8, 2001 for the Crohn's disease indication. In September 2005, with the reassignment of products from the CBER Division of Therapeutic Biologic Medicine Products to the CDER review divisions, the Crohn's disease protocols were consolidated under IND 11197, overseen by the Division of Gastroenterology Products (DGP) and the rheumatic disease protocols remained under IND 9869, overseen by the then Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP). The applicant submitted an End-of-Phase 2 (EOP2) meeting request for the PsA and Axial Spondyloarthritis (AxSpA) indications in March 2009. This meeting request was denied but written responses were provided to the sponsor after consultation was obtained from the Study Endpoints and Labeling Development (SEALD) team regarding the proposed use of patient-reported outcome (PROs) measures in the proposed trials. This feedback was provided in February 2010.

At that time DAARP generally agreed with the proposed trial design in PsA (primary endpoints of American College of Rheumatology 20% improvement response criteria (ACR20) at Week 12 and modified Total Sharp Score (mTSS) at Week 24. The sponsor proposed an initial supplemental application that would include ACR20 and health assessment questionnaire-disability index (HAQ-DI) results and a second application with radiographic outcome results and more extended duration (Week 48) ACR20 and HAQ-DI results. DAARP relayed SEALD comments regarding the (b) (4)



<sup>1</sup> Gladman DD, et al., "Psoriatic arthritis: epidemiology, clinical features, course, and outcome." *Annals of Rheumatic Disease*, 2005, 64:14-17.

At the pre-sBLA meeting for the PsA and AxSpA indications on July 31, 2012, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) agreed that the PsA trial and endpoints appeared to be generally reasonable. Additional detailed discussion took place regarding the analysis of the radiographic endpoint and approaches to handling missing data and extrapolating placebo data for the Week 48 timepoint. Based on their review of the radiographic data, the sponsor proposed to provide post-hoc analyses using an 8 week minimum time interval between radiographs and other imputation methods that were not pre-specified. UCB was allowed to submit all analyses and this would be a review issue.

### 3. CMC/Device

*Primary reviewer: Rashmi Rawat, Ph.D.; Branch chief: Sarah Kennett, Ph.D.*

- **General product quality considerations**

No changes to the marketed product presentation, manufacturing, or controls for certolizumab were proposed in this submission.

- **Facilities review/inspection**

No change to the currently approved facilities was proposed in this submission. There are no outstanding issues that would preclude approval of this sBLA.

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

None.

### 4. Nonclinical Pharmacology/Toxicology

No nonclinical studies were submitted with this sBLA. The nonclinical studies in the development program for certolizumab were submitted in the original BLA for Crohn's Disease.

### 5. Clinical Pharmacology/Biopharmaceutics

*Primary clinical pharmacology reviewer: Liang Zhao, Ph.D.; Clinical pharmacology team leader: Satjit Brar, Pharm.D., Ph.D.*

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.**

The general clinical pharmacology data were reviewed in the original BLA. No clinical pharmacology studies were included in this sBLA and no clinical pharmacology-related labeling changes have been proposed by the sponsor. No clinical pharmacology data were collected in Study PsA001.

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

None.

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical- Efficacy

*Primary clinical reviewer: Suzette Peng, M.D.*

*Primary statistical reviewer: Kiya Hamilton, Ph.D.; Secondary statistical reviewer: Ruthanna Davi, Ph.D.*

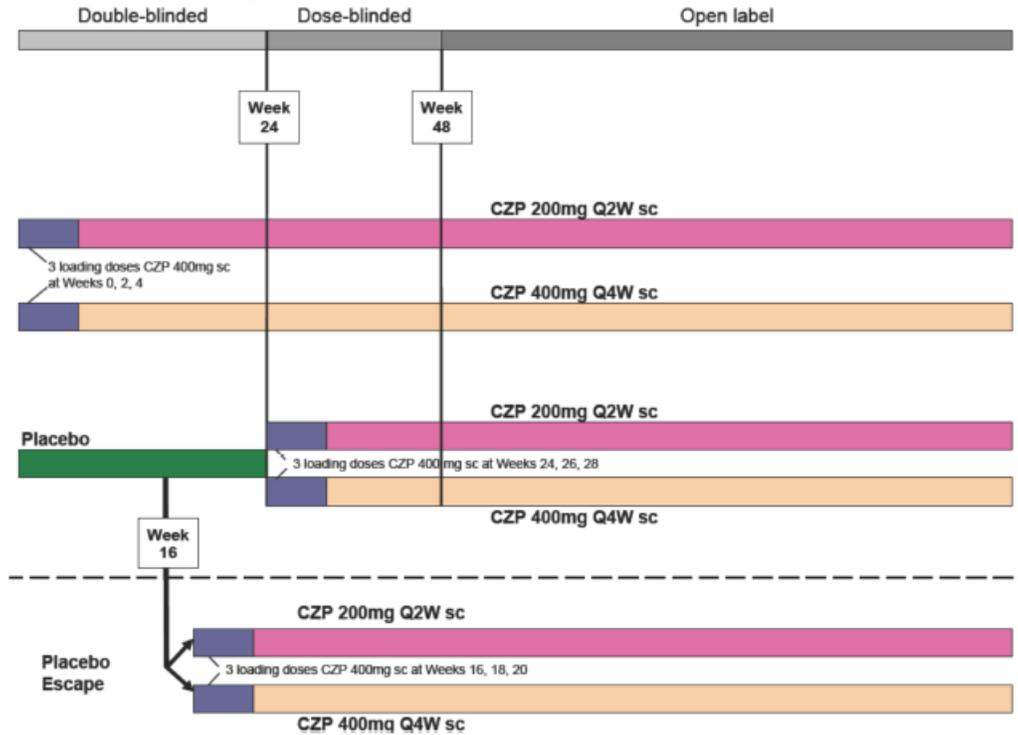
- **Clinical and statistical review of efficacy**

A single study in PsA, PsA001, was conducted (Figure 2 below). This was a multicenter randomized double-blind placebo-controlled study in 393 patients. The study was designed with a 24-week controlled period, where patients received certolizumab 400 mg subcutaneously (sc) at Weeks 0, 2 and 4, followed by 200 mg sc every 2 weeks or 400 mg every 4 weeks or placebo. The doses selected for study in PsA were based on the doses evaluated and shown to be safe and effective for the treatment of patients with RA. Placebo group patients who had not achieved an at least 10% improvement in the number of tender and swollen joints were re-randomized at Week 16 to receive certolizumab at either the 200 mg every 2 week or 400 mg every 4 week regimens (following the 400 mg loading doses at Weeks 16, 18, and 20).

The data cutoff for this submission was May 31, 2012. This submission contains the completed placebo-controlled double-blind treatment period with additional safety data through the data cutoff. Although data from the dose-blind treatment period (through Week 48) are complete, these have not been submitted for review in this application.

The primary efficacy endpoint in PsA001 was the proportion of ACR20 responders at Week 12. The ACR20, ACR50, and ACR70 is defined as a 20%, 50% or 70% improvement from baseline in tender joint count and swollen joint count, and the same level of improvement in at least 3 of the 5 following variables: patient pain on a visual analog scale (VAS), patient global assessment of disease activity on a VAS, physician global assessment of disease activity on a VAS, Health Assessment Questionnaire-Disability Index (HAQ-DI), and C-reactive protein (CRP).

**Figure 1: PsA001 Study Design**



CYP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks; sc=subcutaneous

*Primary Endpoint*

Table 1 below summarizes the results for the primary endpoint of ACR20 responders at Week 12. The primary efficacy analysis utilized a non-responder imputation for missing data. Both the 200 mg Q2W and 400 mg Q4W dose regimens resulted in approximately 30% more ACR20 responders compared with placebo treatment.

**Table 1: Primary Endpoint Results: ACR20 at Week 12 (Randomized Set, Non-Responder Imputation)**

Week 12	Placebo N=136	CYP 200mg Q2W N=138	CYP 400mg Q4W N=135
<b>Responders (%)</b>	33 (24%)	80 (58%)	70 (52%)
<b>Difference between the treatment groups (p-value)</b>		34% (<0.001)	28% (<0.001)

Source: Table 4 of Dr. Hamilton’s statistical review

*Secondary Endpoints*

In order, the ranked secondary endpoints included ACR20 response at Week 24 (200 mg regimen then 400 mg regimen), change from baseline to Week 24 in HAQ-DI (combined 200 mg and 400 mg regimen results), change from baseline to Week 24 in modified Total Sharp

Score (mTSS)(combined 200 mg and 400 mg results), proportion of patients with a Psoriasis Area Severity Index 75% (PASI 75) level of improvement at Week 24 (combined 200 mg and 400 mg results), and change from baseline to Week 48 in mTSS (combined 200 mg and 400 mg results).

Despite its apparent place in the hierarchy, the applicant identified the radiographic endpoint (change from baseline to Week 24 in mTSS) as the second primary endpoint of the trial. The mTSS is a radiographic scoring system that quantifies the extent of bone erosions and joint space narrowing (JSN) for 64 and 52 joints, respectively, with higher scores representing greater damage. The maximum possible scores were 320 for erosions, 208 for JSN, and 528 for the total score. However, patients' scores are typically much lower, because only a fraction of all the possible joints are involved at any given time.

In the applicant's pre-specified analysis, scores for subjects who withdrew for any reason, or subjects with missing Week 24 measurement, or placebo subjects who used rescue medication were linearly extrapolated from the last two radiographs before Week 24 or the early withdrawal or before receiving rescue medication. Missing baseline mTSS measurements were imputed with the minimum value observed, which was 0. If a subject was missing at least two measurements including Week 24, then the missing Week 24 score was imputed with the maximum value observed in this study, which was 356.6. This value was observed in a single patient who was in the CZP 400 mg q4w group. Although linear extrapolation has been used in previous clinical development programs for PsA, the other aspects of this pre-specified analysis plan were unusual and led to an unusual primary analysis result (Table 2 below). The primary analysis result suggests worsening in all treatment groups, and although worst with placebo, the differences are not statistically significant.

**Table 2: Applicant's Pre-specified Analysis of Radiographic Endpoint: Change from Baseline in mTSS at Week 24**

	Placebo*	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W +400mg Q4W
	N=136	N=138	N=135	N=273
<b>Mean change from baseline (SE)</b>	28.9 (7.7)	11.5 (7.6)	25.1 (7.9)	18.3 (6.1)
<b>Difference between treatment groups (p-value)</b>		-17.4 (0.071)	-3.9 (0.688)	-10.6 (0.203)

Source: Cimzia/Active Psoriatic Arthritis PsA001 Double-Blind-Protocol Number PsA001 Table 4.9.1, page 425

\* For the entire placebo group, linear extrapolations are used for subjects escaping to CZP.

Source: Table 10 of Dr. Hamilton's statistical review

The applicant argues that the pre-specified analysis results are not a realistic portrayal of the radiographic results in the cohort, and are physiologically implausible. They also refer to radiographic results seen in trials with other TNF inhibitors in PsA, which did not have this level of worsening (an order of magnitude less), even in the placebo control groups.

The applicant submitted several post-hoc analyses of the radiographic endpoint that yielded results more consistent with those seen in other TNF inhibitor trials in PsA. However, the

FDA statistical team was concerned that the applicant’s post-hoc analyses appeared to have been designed with the goal of achieving the expected results, rather than a rational approach to the missing data. As an alternative, the FDA statistical team tested two straightforward analyses:

- First analysis: For subjects with mTSS measured at just two time points, linear extrapolation was used. Subjects with less than 2 mTSS observations were excluded from the analysis. Although this does not resolve the problem of missing data not being random, this was considered acceptable because the proportion patients who had less than 2 mTSS observations was small.
- Second analysis: This analysis was identical to the first with one exception. Many of the patients with less than 2 mTSS observations (that are excluded in the first analysis) were being counted that way simply because they had escaped. Thus instead of being counted as missing, these patients were included using their observed values (even though these values occurred after escape). This analysis was preferred by the statistical review team as a conservative estimate of the treatment effect because of the likelihood that escaped placebo patients would be expected to have better scores on rescue treatment.

Both these analyses were consistent (see Table 3 below). The 200 mg dose was statistically significantly better than placebo. 400 mg generally trended in the right direction but was not statistically significantly different from placebo.

**Table 3: FDA Post-Hoc Analyses of Radiographic Endpoint: Change from Baseline in mTSS at Week 24**

	Placebo Total N = 136	CZP 200 mg q2w Total N = 138	CZP 400 mg q4w Total N = 135	CZP Combined Total N = 273
<b>FDA Preferred Analysis: Exclusion of patients with &lt; 2 available x-rays; inclusion of escape patient observed data</b>				
Sample Size	n = 123*	n = 130	n = 123	n = 253
Mean change from baseline in mTSS	0.18	-0.02	0.09	0.03
Difference between vs. pbo (p-value)		-0.21 (p = 0.017)	-0.10 (p = 0.261)	-0.15 (p = 0.042)
<b>FDA Post Hoc Analysis 2: Exclusion of patients with &lt; 2 available x-rays; Escape patient data not utilized</b>				
Sample Size	n = 117**	n = 130	n = 123	n = 253
Mean change from baseline in mTSS	0.27	-0.001	0.11	0.05
Difference between vs. pbo (p-value)		-0.27 (p = 0.008)	-0.16 (p = 0.122)	-0.21 (p = 0.016)

\*For patients escaping from placebo to CZP, their observed data on CZP are utilized for calculation

\*\*For patients escaping from placebo to CZP, linear extrapolation is used for calculation

Source: Tables 11 and 12 from Dr. Hamilton's statistical review

Results for other secondary endpoints were robust, and the differences between the CZP groups and placebo were statistically significant (Table 4 below). The proportion of patients with an ACR 20 response at Week 12 (the primary endpoint of PSA001) is included in Table 4 for completeness. Certolizumab treatment was associated with greater improvement compared to placebo for ACR 20/50/70 responses at Week 12 and Week 24, change from baseline in HAQ-DI, and the proportion of patients achieving an at least 0.3 unit improvement (the minimal clinically important difference, or MCID, for the HAQ-DI in PsA<sup>2</sup>) in the HAQ-DI at Week 24.

In the subgroup of patients with at least 3% body surface area (BSA) involved by psoriasis, CZP treatment was associated with an increase in the proportion of patients experiencing a

<sup>2</sup> Mease PJ et al., “Psoriatic arthritis assessment tools in clinical trials.” Ann Rheum Dis 2005; 64 (Suppl II):ii49-ii54

75% improvement in the Psoriasis Area Severity Index (PASI 75); the difference compared with placebo was statistically significant. (b) (4)

**Table 4: Other Secondary Endpoint Results**

Endpoint	Placebo n = 136	CZP 200 mg q2w n = 138	CZP 400 mg q4w n = 135
<b>ACR 20</b>			
Week 12	24%	58%	52%
Week 24	24%	64%	56%
<b>ACR 50</b>			
Week 12	11%	36%	33%
Week 24	13%	44%	40%
<b>ACR 70</b>			
Week 12	3%	25%	13%
Week 24	4%	28%	24%
<b>HAQ-DI, chg from baseline</b>			
Week 24	0.19	-0.54	-0.46
<b>HAQ-DI, pts with <math>\geq 0.3</math> u improvement</b>			
Week 24	15%	49%	48%
<b>PASI 75 (n = pts with <math>\geq 3\%</math> BSA)</b>	<b>n = 86</b>	<b>n = 90</b>	<b>n = 76</b>
Week 24	15%	49%	48%

CZP = certolizumab; both CZP groups received a loading dose of 400 mg at Weeks 0, 2 and 4

pts = patients; PASI 75 = Psoriasis Area Severity Index 75% improvement

BSA = Body Surface Area (affected by psoriasis)

All differences from placebo are statistically significant

Sources: Tables 9, 11-13 from Dr. Peng's clinical review; Tables 5, 6, 8, 14 from Dr. Hamilton's statistical review

- **Includes discussion of notable efficacy issues both resolved and outstanding**

The clinical and statistical teams are in agreement that Study PsA001 provides substantial evidence of the efficacy of certolizumab for treatment of active psoriatic arthritis, based on multiple measures of clinical response, including the primary efficacy endpoint of the proportion of ACR 20 responders at Week 12. Although the applicant's pre-specified analysis for the radiographic endpoint yielded unusual results due to a single outlier, FDA's analyses of the radiographic results using conservative missing data handling methods supported a conclusion of a beneficial treatment effect associated with CZP. The difference compared to placebo was only statistically significant with the CZP 200 mg q2w dose regimen, although the trend for the CZP 400 mg q4w dose regimen was also consistent with a favorable treatment effect.

## 8. Safety

Like other TNF inhibitors, the currently approved certolizumab label contains a boxed warning regarding an increased risk for serious infections (including tuberculosis, invasive fungal, and opportunistic infections) and the observation of lymphoma and other malignancies in children

and adolescents treated with TNF inhibitors. Also consistent with other TNF inhibitors, the Warnings and Precautions section of the label includes serious infections, malignancy, heart failure, hypersensitivity reactions, hepatitis B virus reactivation, neurologic reactions, cytopenias, autoimmunity/lupus-like syndrome, and to avoid live vaccines during treatment. No unique safety signals have been identified for certolizumab apart from the expected concerns observed with TNF inhibitors.

- **Discuss the adequacy of the database, major findings/signals, special studies, etc.**

The bulk of the safety experience with certolizumab has been in the approved indications of Crohn's disease and RA. This experience has been evaluated on an ongoing basis via mandated postmarketing safety assessments as part of the REMS and as part of Section 915 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). The safety profile of certolizumab has been consistent with the safety profile of other TNF inhibitors. In this application, UCB focused on the PsA safety database, with a separate discussion of the accrued safety in other indications.

Overall, the safety profile of certolizumab in PsA appears to be consistent with the safety profile of certolizumab in Crohn's disease and RA. No new safety signals were identified from the PsA clinical development program.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

#### *Deaths*

Two deaths occurred in the double-blind treatment period (through Week 24); both in the CZP treatment arms (one in the 200 mg and one in the 400 mg group). One patient was reported as "sudden death" and the other patient was reported as "cardiac arrest." Four other deaths were reported during the dose-blind (through Week 48) and open-label (after Week 48) periods through the data cutoff date of 31 May 2012. These included breast cancer, lymphoma, cardiac infarction and sepsis as etiologies. Overall, the frequency and types of deaths observed appears consistent with the clinical development program of certolizumab in RA and other TNF inhibitors.

#### *Serious Adverse Events*

CZP treatment was associated with an increased incidence of nonfatal serious adverse events (SAE) compared to placebo during the double-blind treatment period of PsA001. A total of 20 SAE occurred (6%) in the combined CZP group compared to 6 (4%) in the placebo group. The most common SAE were serious infections, which occurred in 1.2% of CZP-treated patients (4 events-herpes zoster, bronchitis, pneumonia x 2, pyelonephritis). Otherwise, there was no predominance of a specific type of SAE.

#### *Discontinuations due to Adverse Events*

The proportion of patients experiencing an adverse event leading to discontinuation during the double-blind treatment period was low, but was higher in the CZP treatment arms (10 AE/3%) than in the placebo group (2 AE/1.5%). There was no predominance of a specific type of AE leading to discontinuation.

#### *Common Adverse Events*

The most common AEs reported with CZP treatment (and higher than placebo) in the double-blind treatment period include nasopharyngitis (~9% of CZP combined group), upper respiratory tract infection (~8% of CZP combined group), elevated liver enzymes and creatine phosphokinase, headache (~4% each), and sinusitis (~3%).

- **Immunogenicity**

Approximately 11% of patients treated with certolizumab developed anti-drug antibodies (ADA) to certolizumab. No clear trends regarding the impact of ADA positivity on efficacy or safety were evident on the basis of the data in this submission.

- **Special safety concerns**

#### *Infections*

In the 24-week double-blind treatment period, a slightly higher incidence of AEs and SAEs due to infection was reported in the CZP treatment arms compared to placebo. Thirty-eight percent of patients in the placebo arm experienced an infection-related AE compared to 43% of patients in the CZP 200 mg q2w arm and 40% of patients in the CZP 400 mg q4w arm. Similarly, 0.7% of patients in placebo experienced a serious infection vs. 1.4% of patients in the CZP 200 mg q2w arm and 1.5% of patients in the CZP 400 mg q4w arm. Overall, the type and frequency of infections was consistent with those observed in the certolizumab RA program and other TNF inhibitor programs.

#### *Malignancies*

During the 24-week double-blind treatment period, a single patient (in the CZP 400 mg q4w treatment group) was diagnosed with a malignancy (Stage 0 cervical carcinoma). In the safety database through the data cut-off of 31 May 2012, 4 additional malignancies were reported—2 patients with breast cancer (one of whom died), 1 patient with thyroid neoplasm, and 1 patient with lymphoma. Overall, the type and frequency of malignancies in the certolizumab PsA program appears to be consistent with certolizumab in RA and with other TNF inhibitors.

#### *Injection site reactions and hypersensitivity*

Certolizumab-treatment was associated with an increased risk of injection site reactions. Injection site reactions occurred in 2% of placebo patients compared to approximately 7% of CZP-treated patients. Pre-specified definitions of anaphylaxis were not used in the program. The applicant categorized reactions as local or systemic and acute vs. delayed. Approximately

1.5% of patients in each group were reported as having a systemic reaction, although more patients in the CZP groups (~1.5% each) had “delayed” systemic reactions compared to placebo (0.7%).

#### *Laboratory abnormalities*

CZP-treatment was associated with a higher incidence of laboratory abnormalities compared with placebo during the double-blind treatment period, including small imbalances in CPK, AST, and ALT; however the incidence was low overall. Approximately 3% of CZP-treated patients had CPK elevations, compared to 2% of placebo-treated patients. Approximately 4% of CZP-treated patients had an elevated ALT compared to 2% of placebo-treated patients. No cases of Hy’s law were observed. These observations were consistent with the laboratory abnormalities observed in the certolizumab RA program.

#### *Demyelinating disorders*

There were no reports of demyelinating or other neurologic disorders.

#### *Other autoimmune disorders*

One case of cutaneous lupus erythematosus occurred in a patient 45 days after starting study medication with CZP 200 mg q2w. Study medication was stopped after the double-blind period because of persistent symptoms.

- **Safety conclusions**

Dr. Peng has concluded that the safety profile of certolizumab in the PsA trial is consistent with the known safety profile of certolizumab from the Crohn’s and RA experience, and no new safety signals have been identified. I concur with Dr. Peng’s conclusions.

- **Discussion of notable safety issues (resolved or outstanding)**

See above.

## **9. Advisory Committee Meeting**

As the fourth TNF inhibitor approved in the class, with results in Crohn’s and RA suggestive of an efficacy and safety profile consistent with other TNF inhibitors, certolizumab was not discussed at an advisory committee meeting for either indication. Similarly, results for the PsA supplemental application did not raise issues meriting discussion at an advisory committee meeting, and no meeting was convened.

## 10. Pediatrics

- **Peds exclusivity board review** - PPSR/WR – Not applicable.
- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, peds assessment**

The applicant requested, and was granted, a full waiver from the Pediatric Research Equity Act (PREA) requirements for the reason that studies are impossible or highly impractical. This is because the subset of children who would develop psoriatic arthritis is difficult to specifically diagnose among patients with juvenile idiopathic arthritis. This was discussed at the Pediatric Review Committee (PeRC) meeting on August 14, 2013, and PeRC was in agreement with granting the waiver. A pediatric study in polyarticular juvenile idiopathic arthritis patients ages 2 to 17 is a postmarketing requirement associated with the approval of certolizumab for RA and is ongoing.

## 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**—Not performed for this supplemental application. Inspections were done with the original BLA and no issues were identified to warrant clinical study site inspections for this submission.
- **Any other outstanding regulatory issues**—Not applicable.

## 12. Labeling

- **Proprietary name**—Already approved as Cimzia.
- **Physician labeling**

The following primary issues have been identified with the proposed labeling changes:

- **Dosage and administration**—the applicant proposed (b) (4)  
(b) (4) 200 mg Q2W is the default maintenance dose in RA (but 400 mg Q4W can also be considered). However, based on a possible increased benefit of the 200 mg q2w dose regimen for the radiographic outcome, with a similar safety profile as the 400 mg q4w dose regimen, the review team believes the dosing for PsA should be worded the same as for RA, with 200 mg q2w being the recommended maintenance dose.
- **Section 14.3 Clinical Studies section for PsA**
  - The applicant proposed inclusion of (b) (4) in labeling; however, (b) (4)

- (b) (4)
- Results for the radiographic endpoint will be based on FDA’s preferred analysis, using observed data for placebo-group patients who crossed over to rescue treatment.
  - The applicant proposed inclusion of results for (b) (4)
- (b) (4)
- For these reasons, these results will not be included in the label.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review**

At the time of this review, labeling negotiations are ongoing with the applicant.

- **Carton and immediate container labels**—No change to the currently marketed presentations are proposed.
- **Patient labeling/Medication guide**—No major changes were proposed by the applicant.

### 13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this supplemental BLA provided agreement can be reached with the applicant on revisions to the proposed labeling changes.

- **Risk Benefit Assessment**

The risk-benefit profile of certolizumab is favorable for the treatment of active psoriatic arthritis in adults. Substantial evidence was provided that certolizumab treatment was associated with improvement in clinical responses, as captured by ACR response criteria, HAQ-DI, and PASI 75, as well as reduction in structural damage, as captured by the change from baseline to Week 24 in mTSS. The safety profile of certolizumab in PsA was consistent with the known safety profile of certolizumab as established in the approved indications of RA and Crohn’s Disease, and also with the safety profile of other TNF inhibitors.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

No changes to the currently approved Risk Evaluation and Mitigation Strategy (REMS) are warranted on the basis of this submission.

- **Recommendation for other Postmarketing Requirements and Commitments**

No postmarketing requirements or commitments are warranted on the basis of this supplemental BLA.

- **Recommended Comments to Applicant**

None.

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/s/  
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SARAH K YIM  
09/09/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125160Origs213**

**MEDICAL REVIEW(S)**

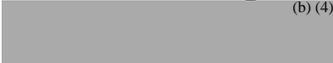
## CLINICAL REVIEW

Application Type Supplemental BLA  
Application Number(s) 125160/213  
Priority or Standard Standard

Submit Date(s) 28 November 2012  
Received Date(s) 29 November 2012  
PDUFA Goal Date 29 September 2013  
Division / Office OND/DPARP

Reviewer Name(s) Suzette W. Peng, MD  
Review Completion Date 26 August 2013

Established Name Certolizumab pegol  
(Proposed) Trade Name Cimzia®  
Therapeutic Class TNF- $\alpha$  inhibitor  
Applicant UCB, Inc.

Formulation(s) Subcutaneous  
Dosing Regimen Loading – 400mg at Week 0,  
2, 4; Maintenance – 200mg  
every 2 weeks  (b) (4)

Indication(s) Psoriatic Arthritis  
Intended Population(s) Adults with active psoriatic  
arthritis

Template Version: March 6, 2009

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

The recommendation on regulatory action is approval of supplemental biological license application (sBLA) 125160/213 for certolizumab pegol for the treatment of adult patients with active psoriatic arthritis, with revisions to the proposed label. The recommended dose should be 400mg initially and at Week 2 and 4, followed by 200mg every other week; for maintenance, 400mg every 4 weeks can be considered. Revisions to the label may include efficacy data to support the treatment of signs and symptoms, improvement of physical function, and inhibition of structural progression in PsA patients.

### 1.2 Risk Benefit Assessment

#### *Overview of the Clinical Program*

UCB, Inc. submitted supplement 213 to BLA 125160 to support the approval of CIMZIA (certolizumab pegol), a biologic TNF $\alpha$  inhibitor, for the treatment of adult patients with active PsA.

UCB submitted 24 weeks of data (data cutoff date 31 May 2012) from ongoing study PsA001. PsA001 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled clinical study to evaluate the efficacy and safety of certolizumab pegol (CZP) on the signs and symptoms, as well as inhibition of structural damage, in PsA patients. The trial consists of a 24-week double-blind, placebo controlled period, followed by a 28-week dose-blind period and then a 56-week open label period. The data included in this supplement cover the 24-week Double-Blind Treatment Period. Two dose frequencies are studied, CZP 200mg every 2 weeks (q2w) and CZP 400mg every 4 weeks (q4w), thus, representing the same cumulative dose.

In the PsA trials, 273 subjects were randomized to certolizumab pegol; after early escape and the week 24 cross-over, 332 subjects were exposed to study drug through the 24-week Double-Blind Treatment Period. The mean number of doses of certolizumab received was 11.2 in the CZP 200mg group and 6.5 in the CZP 400mg group. Through the clinical cutoff date of 31 May 2013, 358 subjects received >6 months of CZP, and 279 subjects received >12 months of CZP for a total of 458.7 patient-years of exposure. In addition, the safety evaluation was supported by a pooled safety database in the adult RA population which includes data for 4049 subjects representing 9277 patient-years of exposure.

### *Summary of Efficacy*

Study PsA001 was designed to evaluate the primary efficacy variables of signs and symptoms and inhibition of structural damage in subjects with PsA. However, based on the prespecified hierarchy of analysis, the primary endpoint is American College of Rheumatology (ACR) 20 Response at Week 12. Change from baseline in modified Total Sharp Score (mTSS) at Week 24 was ranked lower on the hierarchy and, thus, should be considered one of the key secondary endpoints. The other key secondary endpoints included ACR 20 response at Week 24, a measure of physical function (Health Assessment Questionnaire-Disability Index, HAQ-DI) at Week 24, and a measure of skin disease (Psoriasis Area and Severity Index, PASI75) at Week 24.

Based on the primary analysis and multiple sensitivity and secondary analyses, the certolizumab pegol-treated groups show significantly greater proportions of ACR 20 responders than the placebo group. This difference was also seen at Week 12 and 24. Numerically, there were more responders in the subjects who received certolizumab 200mg q2w.

As a measure of physical function, subjects on certolizumab pegol had a significantly greater change in baseline of HAQ-DI at Week 24. Again, numerically there was a greater change in the CZP 200mg q2w group.

The radiographic endpoint did not meet significance by primary analysis. Based on the review, it appears that the prespecified imputation rules may have led to physiologically unrealistic results. However, using post-hoc analyses that were determined appropriate by the Division's statistical team, the radiographic data at Week 24 did show statistical significance with less progression in mTSS scores in the CZP 200mg q2w group than in the placebo group. The subjects who received CZP 400mg q4w also had less progression, but there was not a statistically significant difference from placebo.

Lastly, assessment of PASI75 was used as a measure of skin response. Once again, there were more PASI75 responders in the CZP-treated groups than in the placebo group. Also, like the other endpoints, there were numerically more responders in the subjects who received certolizumab pegol 200mg. (b) (4)



In conclusion, the results of PsA001 support the efficacy of certolizumab pegol in the treatment of active PsA. Certolizumab pegol has a treatment effect on signs and symptoms as well as physical function and inhibition of radiographic progression. Certolizumab pegol 200mg every 2 weeks was associated with a small consistent numerically greater improvement for the evaluated efficacy outcomes compared to the 400 mg every 4 week dose regimen.

### *Summary of Safety*

The review of the clinical safety data indicates that the findings in PsA are consistent with the findings in the known safety profile of certolizumab pegol in the approved indications of RA and Crohn's Disease. In addition, the findings are consistent with the general safety profile of anti-TNF $\alpha$  therapy.

There were 2 deaths in the PsA trials in the double-blind treatment period (both in CZP-treated patients) and a total of 6 deaths through the data cutoff date. The types of deaths (infections, malignancies, cardiac disorders) are consistent with those seen in other trials of biologic immunosuppressives in PsA.

The numbers of nonfatal serious adverse events (SAEs) and AEs leading to discontinuation were higher in the CZP-treated subjects. For both categories of adverse events, the most common SOC was Infections and Infestations. Given that risk of infections is a well-known toxicity of TNF $\alpha$  inhibitors, this is not a new safety signal.

The main areas of safety concern are the same ones from the original BLA and RA supplement – i.e., serious infections, malignancy, cardiovascular (CV) events, immunogenicity and allergic reactions.

Through the end of the reporting period, the exposure-adjusted incidence of serious infections was 1.74 and 3.14 per 100 patient-years for CZP 200mg and CZP 400mg respectively. The rate of serious infections in RA patients on ant-TNF $\alpha$  has been estimated at 5-6 per 100 patient-years (Dixon 2007). Thus, the findings in PsA001 are consistent with what is seen in other TNF inhibitors. Through the data cutoff date, there were 3 opportunistic infections – 2 cases of HIV and 1 case of ophthalmic herpes (nonserious). In addition, there were 8 cases of PPD conversions of which 5 might be consistent with latent TB. There were no cases of active TB through the data cutoff date.

In the Double-Blind Treatment period, there were 2 malignancies (cervical carcinoma stage 0 and breast CA). Through the data cutoff date, there was an additional 4 malignancies (2 cases of breast CA, thyroid CA, lymphoma). Through the data cutoff date, the exposure-adjusted incidence was 0.87 and 1.33 per 100 patient-years for CZP 200mg and 400mg respectively. Overall, these findings are consistent with the experience of other TNF inhibitors in other rheumatic disease.

Through the end of the reporting period, the exposure-adjusted incidence rate of CV events was 2.62 per 100 patient-years for CZP 200mg and 1.80 per 100 subject-years for CZP 400mg. There were no cases of isolated heart failure (i.e., not in the setting of concomitant myocardial infarction). Patients with PsA are at increased risk of CV disease, so these findings do not seem greater than what is expected.

Overall, immunogenicity and hypersensitivity reactions are consistent with what has been seen in other biologic therapy. Through Week 24, 10.8% of subjects exposed to CZP had a positive anti-drug antibody status. The number of injection site reactions is low. Through the controlled portion, there were more local injection site reactions in subjects who received CZP. However, the number of systemic reactions was similar across treatment arms.

In summary, the types and rates of adverse events submitted with this supplement are consistent with those reviewed with the original BLA. No new safety signals have been identified. Exposure-adjusted incidence rates of death, SAEs, serious infections, malignancies are similar to the original BLA. Laboratory abnormalities and outcomes are consistent with the original BLA. Essentially, the types of AEs are consistent with the original BLA and the underlying patient population.

#### *Risk-Benefit Assessment*

This supplemental BLA provides substantial evidence of certolizumab pegol's clinical efficacy in treatment of active PsA in adult patients. In addition, the safety findings in study PsA001 are consistent with the known safety signals for certolizumab pegol and other TNF $\alpha$  inhibitors. There are no new safety signals. Therefore, the overall risk-to-benefit ratio is favorable in the population of patients with active PsA. The results show a treatment effect for signs and symptoms, physical function, and reduction in radiographic progression.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

Certolizumab pegol currently has a Risk Evaluation and Mitigation Strategy (REMS) that was approved in November 2009. The goal of the REMS is (1) to communicate and mitigate the risks associated with CZP therapy by alerting and warning healthcare providers of the recent cases for unrecognized histoplasmosis and other invasive fungal infections associated with concomitant anti-TNF $\alpha$  therapy and (2) educating patients of the serious risks associated with certolizumab pegol therapy. The current REMS is comprised of a Medication Guide and a Communication Plan (including a *Dear Healthcare Provider* letter, a UCB Medical Science Liaison slide presentation, and web-based materials to inform healthcare providers and patients). The first REMS assessment was performed after the cutoff date of 30 November 2009. The second assessment used the cutoff date of 31 March 2011. The final assessment will be performed in May 2014.

Based on this review, the current REMS is adequate.

## 1.4 Recommendations for Postmarket Requirements and Commitments

### *Studies to achieve compliance with PREA*

The juvenile equivalents of psoriatic arthritis are extremely rare because juvenile idiopathic arthritis (JIA) patients do not typically develop sufficient distinguishing features of psoriatic arthritis for this specific diagnosis to be made during childhood. In and of itself, JIA has a low prevalence (between 7 and 400 per 100,000 children). As a subset of JIA, juvenile PsA occurs even less frequently. It is estimated that juvenile PsA accounts for 5-6% of all cases of chronic childhood arthritis. The diagnostic criteria for juvenile PsA has differed in the past, and, based on the criteria used, the incidence has varied, generally estimated around 0.23 cases per 100,000 children per year. Therefore, the Agency has historically granted waivers for pediatric studies for this indication because studies would be highly impractical.

UCB, Inc. seeks a full waiver from pediatric studies for PsA for the above reasons, and this request is reasonable especially because certolizumab pegol has an ongoing pediatric program in JIA. This study (RA0043) is a multi-center, open-label study to assess PK, safety, efficacy in children and adolescents with moderately to severely active polyarticular JIA. Subjects with Juvenile PsA may enroll in this study. This study was submitted in October 2011 and amended in July 2012 and August 2013. A final study report will be submitted in October 2015.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

CIMZIA® is certolizumab pegol (CZP), a humanized fragment antigen binding prime (Fab') conjugated to polyethylene glycol which specifically targets tumor necrosis factor alpha (TNF $\alpha$ , TNF). In binding TNF $\alpha$ , CZP inhibits TNF $\alpha$ 's role as a key mediator of inflammation.

UCB has conducted extensive clinical studies in an effort to develop CZP for multiple indications – rheumatoid arthritis (RA), Crohn's Disease (CD), psoriasis, psoriatic arthritis, and axial spondyloarthritis. CZP first became available in Switzerland on 3 January 2008 for patients with Crohn's Disease following the approval by the Swiss health authority, Swissmedic, on 7 September 2007. The US Food and Drug Administration (FDA) then approved CZP on 22 April 2008 for reducing the signs and symptoms of Crohn's Disease and maintaining clinical response in adult patients with moderately to severely active disease with inadequate response to conventional therapy. The recommended dose in CD is 400mg initially and at Weeks 2 and 4, followed by 400mg every 4 weeks (q4w). CIMZIA was then approved in the US for

treatment of adult patients with moderately to severely active RA on 13 May 2009 (supplemental BLA 125160-80). The approved doses for RA patients are 400mg initially and at Week 2 and 4, followed by 200mg every 2 weeks (q2w); for maintenance dosing, 400 mg every 4 weeks can be considered. The proposed dose for psoriatic arthritis is 400 mg initially and at Week 2 and 4, followed by 200 mg q2w (b) (4)

At this time, in the US, CIMZIA is available as a single-use vial (lyophilized powder for reconstitution, 200mg) or a pre-filled syringe (200mg) for subcutaneous (sc) injection. No change to the currently marketed presentations are being proposed in this supplemental biologics license application (sBLA).

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 presents the approved products for the treatment of psoriatic arthritis (PsA) in the United States. Steroids are not on the list but are also approved for PsA. Compared to RA, there are fewer products approved in the United States to treat PsA.

**Table 1. Approved Products for the Treatment of Psoriatic Arthritis in the United States<sup>1</sup>**

	Product	NDA/BLA (sponsor)	Year Approved for PsA <sup>2</sup>	Characteristics	ROQ
1	Infliximab (Remicade®)	103772 (Centocor)	2005	Monoclonal antibody (TNF inhibitor)	IV
2	Etanercept (Enbrel®)	103795 (Immunex)	2002	Fusion protein (TNF inhibitor)	SQ
3	Adalimumab (Humira®)	125057 (Abbott)	2005	Monoclonal antibody (TNF inhibitor)	SQ
4	Golimumab (Simponi®)	125289 (Centocor)	2009	Monoclonal antibody (TNF inhibitor)	SQ

<sup>1</sup> Steroids are also approved for the treatment of PsA

<sup>2</sup> Infliximab was originally approved in 1998 for Crohn's Disease; etanercept was originally approved in 1998 for RA; adalimumab was originally approved in 2002 for RA; and golimumab was originally approved in 2009 for RA, PsA, and AS.

## 2.3 Availability of Proposed Active Ingredient in the United States

Certolizumab pegol was first approved in the United States in 2008 for Crohn's Disease. In 2009, it was approved for Rheumatoid Arthritis.

## 2.4 Important Safety Issues With Consideration to Related Drugs

CIMZIA currently has the labeled warnings, like the other TNF $\alpha$  inhibitors, of serious infections (including TB, invasive fungal, and other opportunistic), malignancy, heart

failure, hypersensitivity reactions, HBV reactivation, neurologic reactions, cytopenias, autoimmune/lupus-like syndrome, and no live vaccines.

In regards to the class of medication (TNF $\alpha$  inhibitors), the major safety risks with administration of anti-TNF $\alpha$  therapy in the treatment of patients with PsA are the increased incidence of infections and the potential risk of developing malignancy with a specific concern for the potential development of lymphomas.

These and other safety concerns are discussed in detail in Section 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

On 6 March 2009, UCB submitted a Type B meeting request to IND 9869 to obtain concurrence on the clinical development programs in psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA). The Type B meeting was denied, but written responses were provided.

- First, the FDA agreed that the proposed study design for a double-blind, placebo-controlled trial in PsA with primary endpoints of ACR 20 at Week 12 and change from baseline in mTSS at Week 24 would generally be acceptable. In addition, if the trial were successful, the FDA agreed that the trial could support a submission for the indication of treatment of adults with active psoriatic arthritis.
- UCB proposed that one of the endpoints would also be mTSS analysis at Week 48 for which the Week 24 data from the placebo group (who crossed over) would be extrapolated and compared with the Week 48 data for the two CZP dose groups. The FDA found this generally acceptable but commented that the Division was working on re-evaluating the ideal statistical method to support a claim of inhibition of structural damage.

In November 2011, UCB requested that the FDA provide additional comments on the proposed mTSS analysis. At the time, the Division recommended that, if possible, UCB should provide radiographic data on patients regardless of whether the patients withdrew from treatment or early escaped. The FDA recommended performing a retrieved drop out sensitivity analysis using this data.

After completion of the trials, UCB requested a Type B pre-sBLA meeting, which took place on 31 July 2012.

- The FDA agreed that supporting the proposed indication of psoriatic arthritis with ACR 20, 50, 70 responses through Week 24 to be generally acceptable.
- For the Clinical Studies section of the label, the FDA agreed that (1) change from baseline in the ACR components at Weeks 12 (b) (4) to support signs and symptoms and (2) change from baseline in HAQ-DI at Week 24 to support physical function would be generally acceptable.

- UCB proposed a strategy for mTSS analysis and pos-hoc imputation. Also, UCB requested comment on the acceptability of submission of 48 weeks of data for a claim of inhibition of progression of structural damage. The FDA made several comments to these questions with a general agreement that is becoming more difficult to demonstrate a treatment effect in radiographic outcomes given the complexity of recent trial designs. First, the FDA was uncertain about the 8-week time point as a minimum time interval between radiographic measurements since the time point according to the pre-specified analysis plan was 12 weeks. The FDA commented that placebo subjects with 24-32 weeks of extrapolated data might make it difficult to make meaningful comparisons between treatment arms. Lastly, the FDA commented on whether it was necessary to submit 2 supplements and that one complete submission might be acceptable. Most of the other questions (regarding the primary analysis, sensitivity analysis, small number of subjects with no progression) would be review issues.

## **2.6 Other Relevant Background Information**

There was no other relevant background information for this application.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

The supplemental BLA submission was in electronic common technical document (eCTD) format and was adequately organized. There were no major amendments.

### **3.2 Compliance with Good Clinical Practices**

According to the Sponsor, PsA001 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, and other applicable local/regional regulations and guidelines regarding the conduct of clinical studies. A signed informed consent form was obtained for each patient prior to enrollment and IRB approval was obtained by the investigators. UCB conducted audits at 17% of the sites along with co-monitoring visits.

The Office of Scientific Investigations (OSI) was not requested to perform routine audits of clinical sites, as certolizumab pegol is already approved. There were no specific concerns regarding study conduct.

### **3.3 Financial Disclosures**

UCB, Inc. submitted FDA Form 3454 certifying that the Sponsor did not enter into “any financial arrangement” with the overwhelming majority of investigators in the certolizumab pegol studies whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). In addition, the Sponsor certified that each of these investigators was required to disclose to the Sponsor whether the investigator had a proprietary interest in certolizumab pegol or a significant equity interest in the Sponsor as defined in 21 CFR 52.2(b). Finally, the Sponsor certified that no listed investigators was the recipient of significant payments as defined in 21 CFR 54.2(f).

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

No new CMC data were submitted with this supplement 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 Clinical Pharmacology**

No new clinical pharmacology data were submitted with the current supplement for review.

#### **4.4.1 Mechanism of Action**

Certolizumab pegol selectively neutralizes human TNF $\alpha$  bioactivity. Because certolizumab pegol does not contain a fragment crystallizable (Fc) region, it neutralizes

TNF $\alpha$  without inducing complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, or other cytotoxicity such as apoptosis and degranulation. Certolizumab pegol also inhibits the production of inflammatory cytokines by monocytes.

#### 4.4.2 Pharmacodynamics

As noted, no new data were submitted with this supplement in regards to pharmacodynamics (PD) and pharmacokinetics (PK).

Of note, in this study, Dickkopf-related protein 1 (DKK1) and sclerostin levels were collected for exploratory biomarker research. This data were not reviewed with this submission.

#### 4.4.3 Pharmacokinetics

From previously reviewed PK data, it is known that certolizumab pegol plasma concentrations were broadly dose-proportional, and PK observed in patients with Crohn's disease and RA were consistent with those seen in healthy subjects. Following sc administration, peak plasma concentrations of certolizumab pegol were attained between 54 and 171 hours post-injection. CZP has bioavailability of approximately 80% following sc administration compared to IV administration. PEGylation delays the metabolism and elimination of its attached peptide from the circulation by a variety of mechanisms such as decreased renal clearance, proteolysis, and immunogenicity. Certolizumab pegol is an antibody Fab' fragment conjugated with PEG for the purpose of extending the half-life ( $t_{1/2}$ ) of Fab'. The terminal elimination half-life ( $t_{1/2}$ ) was approximately 14 days for all doses tested. The clearance following sc dosing in the RA population was estimated as 21.0 mL/h with inter-subject variability of 30.8% (%CV) and inter-occasion variability of 22.0%.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

The clinical efficacy data to support the current supplement to the original BLA are derived from study PSA001 (Table 2).

**Table 2. Key design of Study PSA001**

Type of Study Study Identifier	Objectives of the Study	Study Design	Test product: Dosage regimen, route of administration	Number of Subjects	Diagnosis of Patients	Duration of treatment	Study Status
Efficacy PsA001	Efficacy and Safety	Randomized, double-blind, parallel-group, placebo-controlled, multicenter trial	<p>PBO or CZP 200mg/mL in prefilled syringe</p> <p>Group I: PBO at weeks 0, 2, 4 followed by PBO every 2 weeks. Then, <b>at week 24, subjects will cross over</b> to receive CZP 400mg at weeks 24, 26, 28 followed by either CZP 200mg every 2 weeks or CZP 400mg every 4 weeks.</p> <p>Group II: CZP 400mg at weeks 0, 2, 4 followed by <b>CZP 200mg every 2 weeks.</b></p> <p>Group III: CZP 400mg at weeks 0, 2, 4 followed by <b>CZP 400mg every 4 weeks.</b></p> <p><b>Early Escape: Week 16.</b> Subjects, who did not achieve at least 10% improvement at both Weeks 14 and 16, were randomized to Group II or III.</p>	<p>409 subjects randomized</p> <p>Group I: 136 subjects</p> <p>Group II: 138 subject</p> <p>Group III: 135 subjects</p> <p><b>Early Escape at Wk 16:</b> Loading (CZP 400mg at <b>wks 16,18,20</b>) + <b>CZP 200mg every 2 wks:</b> 30 subjects</p> <p>Loading (CZP 400mg at <b>wks 16,18,20</b>) + <b>CZP 400mg every 4 wks:</b> 29 subjects</p> <p><b>Crossover at Wk 24:</b> Loading (CZP 400mg at <b>wks 24,26,28</b>) + <b>CZP 200mg every 2 weeks:</b> 28 subjects</p> <p>Loading (CZP 400mg at <b>wks 24,26,28</b>) + <b>CZP 400mg every 4 weeks:</b> 31 subjects</p>	Subjects with active PsA	24 weeks	Ongoing  Data cutoff 31 May 2012

Source: Tabular listing of clinical studies for psoriatic arthritis, psoriasis, and rheumatoid arthritis, Module 5.2  
 Flowchart of subject disposition in PsA001 (data cutoff 31 May 2012), Clinical overview, Figure 1-2, page 6

## 5.2 Review Strategy

The acceptability of using clinical efficacy data from a single study to support the proposed supplement claims after the approval of the original BLA was previously discussed with the Agency and generally agreed upon as discussed in the Regulatory Background section above.

The clinical efficacy data to support the current supplement to the original BLA are derived from a planned analysis of signs and symptoms, physical function, and radiographic data at Weeks 12 and 24. Twenty-four weeks of data are submitted with this submission.

For the safety evaluation, adverse events and markedly abnormal laboratory data are compiled through the data cutoff date of 31 May 2012. In addition, safety data from the RA studies will be used as supportive data.

Details of the review strategy for efficacy and safety are discussed at length in Sections 6.1.1 Methods and 7.1 Methods, respectively.

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Overall Study Design of Study PSA001

Study PSA001 was a Phase 3, multi-center, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol (CZP) in subjects with adult-onset active and progressive psoriatic arthritis (PsA).

The study was divided into 5 periods. Figure 1 illustrates the study design.

**Period 1:** The screening period lasted anywhere from 1 to 5 weeks in order to obtain laboratory data, to verify that the doses of allowed DMARDs, NSAIDs, corticosteroids (if used) are stable, and to enable washout of any medications that are not permitted during the study.

**Period 2:** Week 0 to Week 24 was the double-blind, placebo-controlled period.

Eligible subjects were allocated to the 3 following treatment arms in a 1:1:1 ratio:

- CZP 400mg subcutaneously (sc) at Weeks 0, 2, 4, followed by CZP 200mg sc every 2 weeks (starting at Week 6)
- CZP 400mg sc at Week 0, 2, 4, followed by CZP 400mg sc every 4 weeks (starting at Week 8)
- Placebo

Study treatments (including placebo) were administered by dedicated, unblinded, trained site personnel at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.

The first database lock occurred after completion of the double-blind period (Week 24). The first interim study report was written at this time. Limited UCB personnel became unblinded for purposes of data analysis, but the Investigator and subject remained blinded to treatment assignments. All subjects switched to active treatment after Week 24.

**Period 3:** Week 24 to Week 48 was the dose-blind period for subjects and Investigators. This period was not placebo-controlled.

Subjects originally randomized to placebo were re-randomized in a 1:1 ratio to receive 3 loading doses of CZP 400mg sc at Weeks 24, 26, 28, followed by CZP 200mg every 2 weeks or CZP 400mg every 4 weeks from Week 30 onward. All subjects who were originally randomized to CZP continued to receive the treatment regimen to which they were assigned.

Dedicated, unblinded, trained site personnel administered the study treatments according to the injection scheme. Then, at Weeks 26 and 28, subjects were trained how to self-administer. From Week 30 onwards, all subjects self-administered 1 injection at home every 4 weeks.

The database was locked after completion of the dose-blind portion, and a second interim study report will be written.

**Period 4:** Week 48 to Week 158 is the ongoing, open-label period.

Subjects will continue to receive the same dose regimen of CZP that they received during Period 3. After Week 48, only subjects randomized to CZP 20mg every 2 weeks will administer CZP 200mg every 4 weeks at home. All other injections will be administered (preferably by self-administration) during scheduled visits.

The last dosing visit will be Week 156, and the final study assessments will be performed at Week 158.

**Period 5:** Week 158 to Week 166 is the period for safety follow-up.

All subjects, including those who withdrew from study treatment, will have a Safety Follow-Up visit 10 weeks after their last dose of study medication.

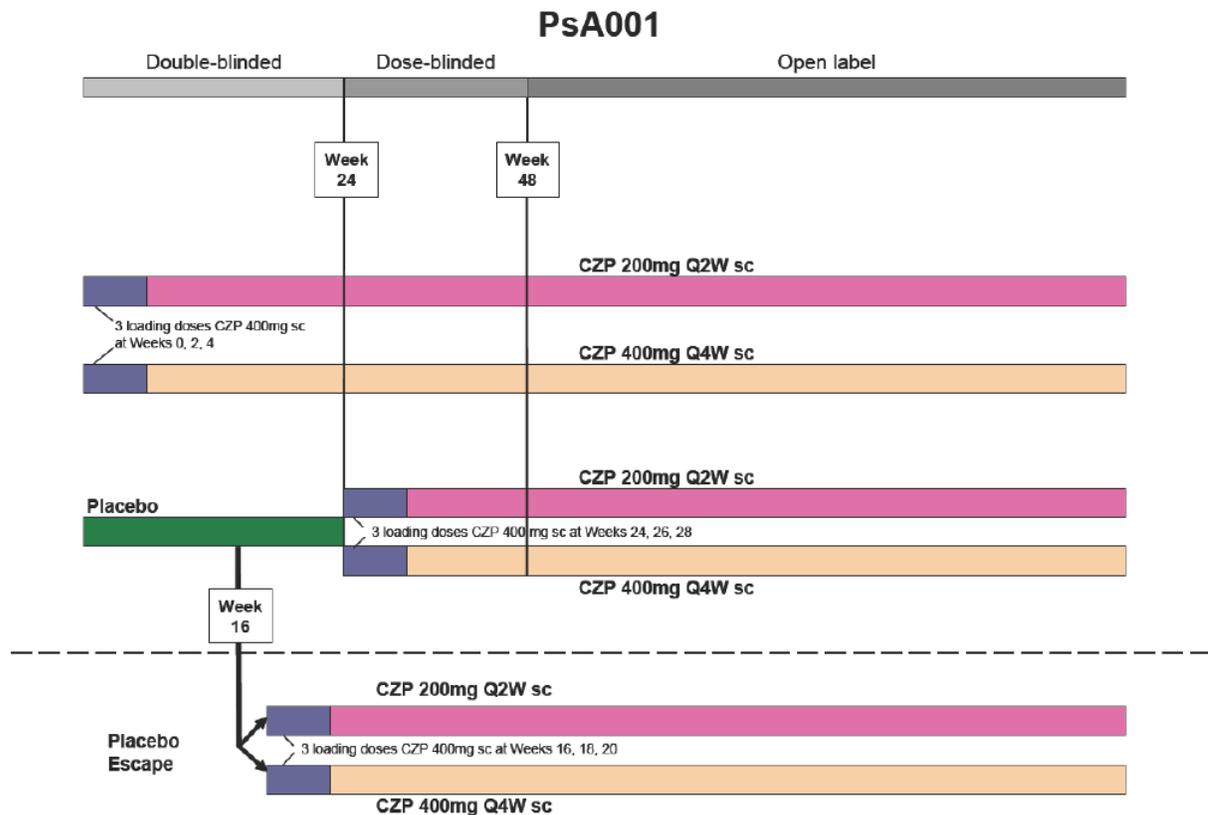
**Escape Treatment:** Week 16

Subjects receiving placebo who did not achieve at least a minimal response (defined as a decrease of at least 10% in the number of tender joints and at least 10% in the number of swollen joints) at both Weeks 14 and 16 were allocated to escape treatment from Week 16 onwards. Escape treatment involved randomization in a 1:1 ratio to CZP 200mg sc every 2 weeks or CZP 400mg sc every 4 weeks. After escape, these subjects continued the escape treatment for the duration of their participation in the study.

Subjects in the active treatment arms (i.e., receiving CZP), even if they qualified for early escape, continued the treatment to which they were originally randomized.

The Interact Voice Response System (IVRS) was used to qualify subjects for early escape at Weeks 14 and 16.

**Figure 1. PsA001 Study Schema**



Source: Protocol Study PsA001 Amendment 3, Section 5.3, page 30.

**Inclusion Criteria**

1. Subject must be at least 18 years-old at the Screening Visit.

2. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent is signed and dated by the subject of designee/witness
3. Subject is considered reliable, willing, and capable of adhering to the protocol, visit schedule, and medication intake
4. Female subjects must be either post-menopausal for at least 1 year, surgically incapable of childbearing, or effectively practicing an acceptable method of contraception. (Abstinence only is not an acceptable method.) Subjects must agree to use adequate contraception during the study and for, at least, 10 weeks after the last dose of study treatment. Similarly, male subjects must agree to ensure that they or their female partner(s) use adequate contraception during the study and for, at least, 10 weeks after the last dose of study treatment.
5. Subject must have a diagnosis of adult-onset PsA (as defined by the CASPAR criteria, defined in Table 3) for at least 6 months.
6. Subject must have active psoriatic skin lesions or a documented history of psoriasis.
7. Subjects must have active arthritis.
  - $\geq 3$  tender joints at Screening and Baseline
  - $\geq 3$  swollen joints at Screening and Baseline
  - At least one of the two following criteria during screening:
    - ESR  $\geq 28$  mm/hr (Westergren)
    - CRP  $>$  upper limit of normal (ULN)
8. Subjects must have failed 1 or more DMARDs.

**Table 3. CASPAR Criteria**

CASPAR criteria

**Inflammatory articular disease (joint, spine, etheseal) AND ≥3 points of the following 5 categories:**

Category	Definition	Points
<b>Evidence of psoriasis (1 of the following):</b>		<b>2 points</b>
<b>Current psoriasis</b>	Psoriatic skin or scalp disease present today as judged by a dermatologist or rheumatologist	
<b>Personal history of psoriasis</b>	A history of psoriasis that may be obtained from the patient, family physician, dermatologist, rheumatologist, or other qualified health care provider	
<b>Family history of psoriasis</b>	A history of psoriasis in a first- or second-degree relative according to patient report	
<b>Psoriatic nail dystrophy</b>	Typical psoriatic nail dystrophy, including onycholysis, pitting, and hyperkeratosis, observed on current physical exam	<b>1 point</b>
<b>A negative test for rheumatoid factor</b>	By any method except latex but, preferably, by ELISA or nephelometry, according to the local laboratory reference range	<b>1 point</b>
<b>Dactylitis (1 of the following):</b>		<b>1 point</b>
<b>Current dactylitis</b>	Swelling of the entire digit	
<b>History of dactylitis</b>	A history of dactylitis recorded by a rheumatologist	
<b>Radiologic evidence of justa-articular new bone formation</b>	Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot	<b>1 point</b>

Source: Protocol Study PsA001 Amendment 3, Appendix, Table 17:1, page 89

**Exclusion Criteria**

Subjects were not permitted to enroll if any of the following criteria were present.

1. The subject has previously participated in this study or has previously received CZP treatment in or outside of another clinical study.

2. The subject has participated in another study of a medication or a medical device under investigation within the last 3 months or is currently participating in another study of a medication or medical device under investigation.
3. Subject has a history of chronic alcohol abuse (more than 14 drinks/units per week for women and 21 drinks/units for men) or drug abuse within the last year.
4. Subject has any medical or psychiatric condition (according to DSM criteria) that, in the opinion of the Investigator, can jeopardize or compromise the subject's ability to participate in the study.
5. Subject has a known hypersensitivity to any component of CZP and placebo or has a history of an adverse reaction to polyethylene glycol (PEG).

PsA disease-related exclusions

6. Subjects must not have a diagnosis of any other inflammatory arthritis (e.g., RA, sarcoidosis, systemic lupus erythematosus) or a known diagnosis of fibromyalgia.
7. Subjects must not have a secondary, noninflammatory condition (e.g., osteoarthritis) that, in the Investigator's opinion, is symptomatic enough to interfere with evaluation of the effect of study drug on the subject's primary diagnosis of PsA.

Prior medications exclusions

8. Table 4 lists the excluded medications from the study.

**Table 4. Medication Exclusions**

<b>Drug Class</b>	<b>Dose</b>	<b>Exclusion Criteria</b>
<b>Analgesics (e.g., acetaminophen)</b>	Any dose	Any ad hoc use in the 24 hrs prior to the Baseline visit Stable doses of analgesics are permitted.
<b>NSAIDs/COX-2 inhibitors</b>	Any dose	Any change in dose regimen in the 14 days prior to the Baseline visit
<b>Corticosteroids (oral)</b>	Maximum allowed: ≤10 mg daily total prednisone equivalent	Any change in dose in the 28 days prior to the Baseline visit
<b>Corticosteroids (intra-muscular, intravenous, intra-articular)</b>	Any dose	Use in the 28 days prior to the Baseline visit
<b>Hyaluronic acid (ia)</b>	Any dose	Use in the 28 days prior to the Baseline visit
<b>DMARDs: hydroxychloroquine, azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil</b>	Any dose	Use in the 28 days prior to the Baseline visit
<b>DMARDs: sulfasalazine (SSZ), methotrexate (MTX), leflunomide (LEF)</b>	<b>Maximum allowed: SSZ ≤3g daily MTX ≤25 mg weekly LEF ≤ 20 mg daily</b>	- Use initiated and/or change in the dose regimen in the 28 days prior to the Baseline visit - Change in the route of administration for MTX (im, sc, po) in the 28 days prior to the Baseline visit - Use of DMARD combination therapy  If combination therapy was being used prior to the Baseline visit, - MTX or SSZ must be discontinued ≥28 days prior to Baseline visit. - LEF must be discontinued ≥6 months prior to the Baseline visit or washed out with cholestyramine ≥28 days prior to Baseline visit.
<b>Biologics: infliximab (IFX), adalimumab (ADA), etanercept (ETN), golimumab (GOL), abatacept (ABA)</b>	Any dose	For IFX, ADA, GOL, and ABA, any use within the 3 months prior to the Baseline visit.  For ETN, use within the 28 days prior to the Baseline visit.
<b>Other biologics: anti-CD20, tocilizumab, certolizumab pegol (CZP)</b>	Any dose	Any exposure history
<b>Prior therapy for Psoriasis</b>		
<b>Systemic treatment (non-biologics)</b>	Any dose	Use within 28 days prior to the Baseline visit
<b>Phototherapy</b>	Any dose	Use within the 28 days prior to the Baseline visit
<b>Topical agents</b>	Any dose	Use within 14 days prior to the Baseline visit
<b>Biologics: alefacept, efalizumab, ustekinumab</b>	Any dose	Any use within the 3 months prior to the Baseline visit

Source: Protocol Study PSA001 Amendment 3, Tables 6:1 and 6:2, pages 35-36

Previous clinical studies and previous biologic therapy exclusions

- Subjects must not have received any nonbiologic therapy for PsA not listed above within or outside a clinical study in the 3 months or within 5 half-lives prior to the Baseline visit (whichever is longer).

10. Subjects must not have received experimental biologic agents other than those listed in Table 4.
11. Subjects must not have received previous treatment with a PEGylated compound that resulted in a severe hypersensitivity reaction or an anaphylactic reaction.
12. Subjects may not have been exposed to more than 1 TNF-antagonist prior to the Baseline visit and may not be a primary failure to any TNF-antagonist (defined as NO response within the first 12 weeks of treatment with a TNF-antagonist).
13. Subjects may not have been exposed to more than 2 previous biologic response modifiers for PsA or psoriasis.

Medical history exclusions

14. Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the study or within 3 months following the last dose of investigational product
15. Subjects with a history of chronic or recurrent infections (more than 3 episodes requiring antibiotics/antivirals during the preceding year), recent serious or life-threatening infection with 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 symptoms that may indicate 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 include atypical 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
      - Time spent in a health care delivery setting
      - Time spent in an institutional setting
  - c. Latent TB infection – e.g., subjects who do not meet criteria for “a” or “b” but do meet any of the following criteria (regardless of prior TB treatment)
    - Current PPD positive (test performed ≤3 months prior to Screening)
    - Previously documented history of a severe positive PPD reaction (test performed >3 months prior to screening) *AND*

- Elispot (performed  $\leq 3$  months prior to Screening) positive or indeterminate *OR*
  - QuantiFERON (performed  $\leq 3$  months prior to Screening, only if Elispot unavailable) positive or indeterminate
  - Subjects with no documented history of a severe positive PPD test can only receive the PPD test for Screening
  - Exception from “c” is permitted only if treatment for latent TB infection is initiated or has been initiated at least 4 weeks prior to study drug administration and treatment is still ongoing at time of study entry
  - A positive PPD is defined as  $\geq 5$  mm induration 48 to 72 hours after intradermal injection of 5TU 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 reported from elsewhere must be documented with exact induration measurement (if performed  $\leq 3$  months prior to Screening)
  - Treatment for latent TB infection includes isonicotinic acid hydrazide/isoniazid (INH) therapy for 9 months (with vitamin B6). Another latent TB infection treatment regimen should be considered if the subject is living in or has recently emigrated from a country with a high endemic rate of INH-resistant or multi-drug resistant TB.
17. Subjects with concurrent acute or chronic viral hepatitis B or C or with known human immunodeficiency virus (HIV) infection
  18. Subjects with known history of or current clinically active infection with *Histoplasma*, *Coccidioides*, *Paracoccidioides*, *Pneumocystis*, nontuberculous mycobacteria, *Blastomyces*, or *Aspergillus*
  19. Subjects with a history of an infected joint prosthesis at any time with that prosthesis still in situ
  20. Subjects receiving any live (or attenuated live) vaccination within the 8 weeks prior to Baseline. Inactivated influenza and pneumococcal vaccines are allowed, but nasal influenza vaccination is not permitted.
  21. Subjects 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 or subjects who are permanently bedridden or wheelchair-bound)
  22. Subjects with a history of a lymphoproliferative disorder including lymphoma or current signs/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 (status post successfully surgical treatment more than 5 years prior to Screening) may be included.
  24. Subjects with class III or IV congestive heart failure (CHF) as per New York Heart Association (NYHA) 1964 criteria

25. Subjects with a history (or suspected history) of demyelinating disease of the central nervous system (e.g., multiple sclerosis or optic neuritis)
26. Subjects who have had a major surgery (including joint surgery) within the 8 weeks prior to Screening or who are planning surgery within 6 months after entering the study
27. Subjects with a current or recent history of severe, progressive, and/or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, or neurologic disease (as determined by the Investigator)
28. Subjects with clinically significant laboratory abnormalities – e.g., liver associated enzymes >2 x upper limit of normal (ULN), creatinine (SCr) >ULN, or white blood cell count (WBC) <3.0 x 10<sup>9</sup> L
29. Subjects with any other condition which would make the subject unsuitable for inclusion in this study (in the Investigator's judgment)

#### *Concomitant Medications*

All medications (including over-the-counter products and nutraceuticals) taken by a subject must be documented at Screening or at any time during the course of the study. A record including the drug name, dose, date(s) of administration, and indication for use must be kept in the clinic chart and the Case Report Form (CRF).

Table 4 lists medications that are excluded and some that were allowed.

To reiterate, the following medications for PsA were allowed during the study from Baseline onward:

- NSAIDs/COX-2 inhibitors
  - Stable doses for 2 weeks prior to arthritis assessment
- Analgesics (e.g., acetaminophen and narcotics) will be permitted except ad hoc as needed (prn) usage within the 24-hours period prior to any assessments.
- Corticosteroids
  - Oral
    - Maximum allowed ≤10 mg daily total prednisone equivalent
    - Subjects are 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 study, 1 ia injection of ≤50 mg prednisone equivalent may be given every 4 months (at most)
  - Intravenous (IV)
    - Only after the first 48 weeks of the study, iv hydrocortisone may be administered for stress dosing prior to surgical procedure
- Specific DMARDS

- SSZ – maximum  $\leq 3$  g daily
- MTX – maximum  $\leq 25$  mg weekly
- LEF – maximum  $\leq 20$  mg daily
- No change in dose or dose regimen is allowed during the first 48 weeks of the study except for difficulties with tolerance at which time the DMARD may be decreased (not discontinued).
- Any changes in dose can be made after the first 48 weeks of the study.
- No changes in the route of administration (oral, intramuscular, subcutaneous) of MTX are permitted in the first 48 weeks of the study.
- Phototherapy and/or topical agents for psoriasis are permitted after the first 48 weeks of the study.
- Live vaccines are not recommended for subjects receiving anti-TNF $\alpha$  therapy.
  - If, after weight risks and benefits, the clinician wishes to give a live organism-based immunization, the subject must be withdrawn from the study prior to vaccine administration. Vaccine administration will need to be recorded in the CRF.

#### *Randomization and Blinding*

An interactive voice response system (IVRS) was used for subject registration, randomization, and treatment administration. For enrollment and randomization, the study investigator contacted the IVRS and gave brief details of the subject. The IVRS then assigned each subject with a unique number. This unique number was then used in all future communications between the investigator and IVRS. During the study, the IVRS medication kit numbers were based on the randomization number. Subjects were allocated to treatment in a 1:1:1 ratio (CZP 200mg q2wks: CZP 400mg q4wks: placebo), and randomization was stratified by site and by prior anti-TNF $\alpha$  exposure. Placebo subjects who early escaped were re-randomized at Week 16 in a 1:1 ratio (CZP 200mg q2wks: CZP 400mg q4wks) stratified by prior anti-TNF $\alpha$  exposure. Placebo subjects who were eligible for cross-over at Week 24 were also re-randomized in a 1:1 ratio (CZP 200mg q2wks: CZP 400mg q4wks) stratified by prior anti-TNF $\alpha$  exposure.

PSA001 was double-blind and placebo-controlled through the first 24 weeks. After the last subject completed the double-blind period, the database was locked (31 May 2012), and treatment codes were exposed to UCB personnel (except operational staff working on the study). From Week 24 onward, all subjects will be treated with CZP, but investigators and subjects remained blind to the CZP dose regimen until the subject reached the Week 48 visit. After the last subject completed the dose-blind period, the database was locked again, and a second interim study report was written. After Week 48, all subjects will be treated with open-label CZP.

During the double-blind portion of the study, all staff associated with the Sponsor, investigator site, and contract research organization remained blinded. The only exceptions to blinding were the sponsor clinical study supplies coordinator, packager, and qualified person; pharmacy monitors that monitor unblinded pharmacy documentation; sponsor pharmacovigilance staff managing SAEs; laboratory staff analyzing blood samples for CZP plasma concentrations and anti-CZP antibodies; and site study drug administrator. In the event of a medical emergency, IVRS could be called, and the treatment arm to which the subject was allocated can be determined. UCB, Inc. or its representative and the medical monitor should be contacted prior to any unblinding. If the blind is broken, information surrounding the event (date, reason, etc.) should be recorded.

#### *Schedule of Assessments*

Details of the schedule of assessments are listed in Table 55 in section 9.4.

#### *Efficacy Endpoints*

PSA001 had several efficacy variables. These variables are defined in detail in Appendix 9.5. Efficacy variables that are not part of this review will not be further defined. The pre-specified sequence of analysis is presented below in the summary of the statistical analysis plan (SAP).

#### *Major Efficacy Endpoints*

- American College of Rheumatology 20% response criteria (ACR 20) responders at Week 12 (Primary endpoint)
- Change from baseline in mTSS at Week 24 (Major secondary endpoint)

#### *Key Secondary Efficacy Endpoints*

- ACR 20 responders at Week 24
- Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24
- Psoriasis Area and Severity Index 75% response (PASI75) responders at Week 24

#### *Other Secondary Efficacy Variables*

- ACR 20 responders at Weeks 1, 2, 4, 8, 16, 18, and 20
- American College of Rheumatology 50% response criteria (ACR 50) responders at Weeks 1, 2, 4, 8, 12, 16, 18, 20, and 24

- American College of Rheumatology 70% response criteria (ACR 70) responders at Weeks 1, 2, 4, 8, 12, 16, 18, 20, and 24
- Change from baseline in all individual ACR core components at Weeks 1, 2, 4, 8, 12, 16, 18, 20, and 24
  - Swollen joint count (66 joints)
  - Tender joint count (68 joints)
  - HAQ-DI (except for Week 24, which is a key secondary variable)
  - Patient's Assessment of Arthritis Pain (PAAP) visual analogue scale (VAS)
  - Patient's Global Assessment of Disease Activity (PtGADA) VAS
  - Physician's Global Assessment of Disease Activity (PhGADA) VAS
  - C-reactive peptide (CRP)
- Change from baseline in mTSS at Week 12
- Change from baseline in the erosion score of mTSS at Weeks 12 and 24
- Change from baseline in the joint space narrowing (JSN) score of mTSS at Weeks 12 and 24
- PASI75 responders at Weeks 1, 2, 4, and 12
- Psoriasis Area and Severity Index 90% response (PASI90) responders at Weeks 1, 2, 4, 12, and 24
- Physician's Global Assessment of Psoriasis (PGAP) responders at Weeks 12 and 24
- Change from baseline in the Leeds Dactylitis Index (LDI) at Weeks 12 and 24
- Change from baseline in the Leeds Enthesitis Index (LEI) at Weeks 12 and 24
- Change from baseline in the Fatigue Assessment Scale (FAS) at Week 12 and 24
- Change from baseline in the Short-Form 36-item Health Survey (SF-36) Physical Component Summary (PCS) at Weeks 4, 8, 12, 16, 20, and 24
- Change from baseline in SF-36 Physical Function domain at Weeks 4, 8, 12, 16, 20, and 24
- Change from baseline in SF-36 Mental Component Summary (MCS) at Weeks 4, 12, and 24
- Change from baseline in Psoriatic Arthritis Quality of Life (PsAQoL) at Weeks 12 and 24
- Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Weeks 1, 2, 4, 8, 20, and 24
- Scores of individual questions of the Work Productivity Survey (WPS) at Baseline, Weeks 4, 12, and 24

#### *Other Efficacy Variables*

- HAQ-DI responders at Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 24
- PAAP-VAS responders at Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 24
- PtGADA-VAS responders at Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 24

- PASI75 responders at Weeks 8, 16, and 20
- PASI90 responders at Weeks 8, 16, and 20
- Change from baseline in PASI at Weeks 1, 2, 4, 8, 12, 16, 20, and 24
- Psoriasis Area and Severity Index 50% response (PASI50) and Psoriasis Area and Severity Index 100% (PASI100) responders at Weeks 1, 2, 4, 8, 12, 16, 20, and 24
- PGAP response (by category) at Weeks 1, 2, 4, 8, 16, and 20
- PGAP responders (response of “clear” or “almost clear”) at Weeks 1, 2, 4, 8, 16, and 20
- Change from baseline in the LDI at Weeks 1, 2, 4, 8, 16, and 20
- Change from baseline in the LEI at Weeks 1, 2, 4, 8, 16, and 20
- Change from Baseline in the FAS at Weeks 1, 2, 4, 6, 8, 10, 16, 18, and 20
- FAS responders at Weeks 1, 2, 4, 6, 8, 10, 12, 16, 18, 20, and 24
- SF-36 (PCS) responders at Weeks 4, 8, 12, 16, 20, and 24
- Change from baseline in SF-36 (MCS) at Weeks 8, 16, and 20
- SF-36 (MCS) responders at Weeks 4, 8, 12, 16, 20, and 24
- Change from baseline in SF-36 domains at Weeks 4, 8, 12, 16, 20, and 24
- Change from baseline in PsAQoL at Weeks 1, 2, 4, 8, 16, 18, and 20
- Scores of the individual questions of the WPS at Weeks 8, 16, and 20
- Psoriatic Arthritis Response Criteria (PsARC) responder at Weeks 1, 2, 4, 8, 12, 16, 20, and 24
- Disease Activity Score-28 joint count (DAS28[CRP]) at Weeks 1, 2, 4, 8, 12, 16, 18, 20, 24:
  - Change from baseline
  - Disease activity classification
  - European League Against Rheumatism (EULAR) response
- Change from baseline in modified Nail Psoriasis Severity Index (mNAPSI) score (in the subgroup of subjects with psoriatic nail disease at baseline) at Weeks 4, 8, 12, 16, 20, and 24

#### Pharmacokinetic (PK) and Pharmacodynamic (PD) Variables

- CZP plasma concentrations at baseline and Weeks 1, 2, 4, 12, 16, 24, and, thereafter, every 24 weeks to study completion/withdrawal visit and at safety follow-up visit (10 weeks after last dose of study drug)
- Anti-CZP antibodies at baseline and Weeks 1, 2, 4, 12, 16, 24, and, thereafter, every 24 weeks to study completion/withdrawal visit and at safety-follow-up visit (10 weeks after last dose of study drug).
- Dickkopf-related protein 1 (DKK1) and sclerostin levels may be analyzed for exploratory biomarker research using selected samples collected for measurement of CZP plasma concentration

### *Sample Size Determination*

The sample size was determined on the larger of 2 estimates for the primary variables. Calculations were based on anticipated differences between the CZP-treated groups and placebo-treated groups in the percentage of subjects with an ACR 20 response at Week 12 and in the change from baseline in mTSS at Week 24. The significance level of 5% for ACR 20 response at Week 12 was not further adjusted since testing of mTSS at Week 24 remained conditional on the ACR 20 at Week 12 being significant for both group considerations.

Based on published data from other anti-TNF $\alpha$ , the Sponsor anticipated that the difference from placebo for the active treatment groups in mean change from baseline in the mTSS would be greater than 1.0. Therefore, a sample size of 130 for each of the 3 treatment groups would be sufficient to detect statistically significant differences in the mean change from baseline in the mTSS between the combined active and placebo group with at least 95% power, assuming a SD of 2.4 points. This sample size is sufficient to detect a statistically significant difference between CZP and placebo at Week 48 with 90% power (and 80% for individual doses), assuming a difference of 2.0 and a SD of 5.6 and applying linear extrapolation. For each treatment group comparison with placebo in the ACR 20 response rate at Week 12, the power is 99%, assuming a difference of 25% (CZP groups 40% and placebo 15%).

Lastly, the study is powered for the primary variable. Other variables from the hierarchical test procedure were not used.

### *Statistical Methods*

For the purposes of analysis, there were several defined sets of data.

- Enrolled Set consists of all subjects who have given informed consent.
- **Randomized Set (RS) consists of all subjects randomized into the study. This is the primary analysis set for efficacy following the intention-to-treat principle.** For efficacy evaluation over time, both RS with imputation and RS without imputation (called the Observed Case, OC) are used.
- Safety Set (SS) consists of all subjects in the RS who received at least 1 dose of study medication.
- Full Analysis Set (FAS) consists of all subjects in the RS who received at least 1 dose of study medication, have a valid baseline measurement of both main efficacy measurements (ACR 20 and mTSS variables), and have a valid post-baseline efficacy measurement (of these same two variables). The ACR measurement must be obtained through Week 12, and the mTSS through Week 24.

- Per-Protocol Set (PPS) consists of the subjects in the FAS who completed a minimal exposure of 12 weeks of the treatment regimen without any major protocol deviations. Post-baseline deviations do not exclude the subject from analysis with this set, but it does exclude that subject's data.
- There are Completer Sets (CSs). The first CS (CS1) consists of subjects in the FAS who completed 24 weeks of the treatment regimen with valid 24-week measurements. The second CS (CS2) consists of placebo-treated subjects who completed 24 weeks of placebo treatment with valid 24-week measurements and CZP-treated subjects who completed 48 weeks of CZP treatment with valid 48-week measurements. Because no imputations are associated with this set, the CSs helped to investigate the robustness of the results. However, there could be bias, as the CSs only included placebo subjects who did not meet protocol definition for escape.

All statistical analyses were performed using SAS (STATISTICAL ANALYSIS SYSTEM). In general, summary statistics (n [number of available measurements], arithmetic mean, SD, median, minimum, maximum) for quantitative variables and frequency tables for qualitative variables were presented by treatment group. For purposes of analysis, the "baseline value" is the last valid measurement before study medication.

Two interim analyses were planned. (1) After completion of the last subject of the double-blind period (Week 24), the database was locked, and the data cutoff date was 31 May 2012. A first interim study report was written at this time. Some UCB personnel were now able to access the treatment codes, thus breaking the blind. However, the Investigators and subjects remained blind to the assigned CZP dose regimen until Week 48. (2) After completion of the last subjects of the dose-blind period (Week 48), the database was locked, and a second interim analysis report was written. After Week 48, subjects would enter the open-label portion of the study through Week 156.

### Efficacy Analyses

The primary analysis of the primary variables was performed using the RS with imputation of missing variables. However, for subjects who were not treated or did not have any efficacy measurements, the RS might give diluted treatment effect estimators. Therefore, the FAS (with imputations), PPS (with imputations), and CS are utilized for sensitivity analyses. In summary, all the analyses described below were primarily performed on the RA, but the same analyses were applied in a more exploratory manner for the other data sets (FAS, PPC, and CS).

For the two primary variables, subgroup analyses looked at age, gender, race, duration of disease, region, concomitant use of allowed DMARDs, and prior anti-TNF $\alpha$  therapy.

**ACR 20 response at Week 12:**

The difference in ACR 20 response rates in the 2 CZP-treated groups and placebo was analyzed using a standard 2-sided Wald asymptomatic test with a 5% alpha level. The corresponding 95% confidence intervals (CIs) for the differences were constructed using the asymptomatic standard errors (asymptomatic Wald confidence limits).

For primary analysis, subjects, who withdrew for any reason before Week 12 or who have missing data at Week 12, were considered to be nonresponders.

For secondary analysis, logistic regression with factors for treatment, region, and prior anti-TNF $\alpha$  therapy was performed. Treatment effects were estimated using odds ratios; corresponding

**Change from baseline to Week 24 in mTSS:**

Comparison between placebo and the combined CZP-treated groups was performed using an analysis of covariance (ANCOVA) model with treatment, region, and prior anti-TNF $\alpha$  therapy as factors and baseline mTSS as covariate. Estimates of the treatment effect were made based on adjusted means, and a 95% CI was also constructed.

See “Handling of Dropouts or Missing Data” below for the approach toward subjects who withdrew before Week 24, subjects who have missing Week 24 measurements, and placebo subjects who early escaped. In addition, for subjects who early escaped, another more conservative approach was utilized. Placebo escape subjects at Week 24 will have their 24-week CZP measurement used for group comparison. This approach could give results favoring the placebo group.

Some of the pre-specified analyses (as defined in the statistical analysis plan, SAP) led to physiologically unrealistic changes in mTSS. The Sponsor attempted to correct these implausible findings with post-hoc analyses. These post-hoc analyses will further discussed in Section Analysis of Secondary Endpoint(s).

Secondary analyses of the mTSS were performed by log transformation and rank transformation of the mTSS data using the same ANCOVA model as above and by applying the nonparametric Wilcoxon test, including Hodges-Lehmann estimates and the corresponding CIs.

**Other efficacy endpoints:**

- ACR 20 response at Week 24

Analysis was essentially the same as that for ACR 20 response at Week 12. Subjects who withdrew before Week 24 were considered nonresponders. Subjects who have missing data at Week 24 were also counted as nonresponders for that particular visit. Placebo subjects who early escaped were counted as nonresponders from the time that early escape therapy was initiated.

- Change from baseline in HAQ-DI at Week 24

The HAQ-DI was compared between treatment groups using an ANCOVA. The model included baseline score, treatment group, region, and prior anti-TNF $\alpha$  therapy. For any missing post-baseline values, LOCF approach was applied. For placebo subjects who early escaped, the last observation prior to escape would be carried forward to Week 24.

- PASI75 at Week 24

PASI75 at Week 24 was analyzed with the same approach as that for ACR20. Therefore, subjects who withdrew before Week 24 were considered nonresponders. Subjects with missing data at Week 24 were counted as nonresponders for that respective visit. For subjects who escaped early, the response at Week 12 was used from the time that escape therapy was initiated.

- Change from baseline in mTSS at Week 48

The same ANCOVA model that was used for the Week 24 assessment was used. See “Handling of Dropouts or Missing Data” below for details of approach toward subjects with missing measurements.

The approach toward efficacy analyses is discussed in more detail in Section 6.1.1 Methods.

#### Sensitivity Analyses of the Primary Efficacy Variables:

Three sensitivity analyses were performed on the primary efficacy variables. These analyses were performed on the RS only.

The first sensitivity analysis involved removing the outliers. Outliers were defined as observations where the residuals were outside the  $\pm 3$  SD window in the ANCOVA for the mTSS.

For the second sensitivity analysis, subjects who were affected by potential unblinding were removed directly or indirectly from analysis. There was some concern that some investigators may have potentially been unblinded at Weeks 16 and 24 to some subjects' treatment assignments. These subjects were identified by Clinical Quality Assurance after unblinding of the study.

The third sensitivity analysis was performed by removing data from subjects who should have withdrawn from the study because of rescue medication intake but did not. These subjects were handled as early withdrawals at the time rescue medication was initiated. The prohibited rescue medications included any of the medications listed in the exclusion criteria (Table 4. Medication Exclusions). The new “missing” values were imputed in a similar approach as the primary analysis of primary variables.

The first and second sensitivity analyses were performed for the change from baseline in mTSS using the ANCOVA with linear extrapolation and with the retrieved drop-out approach. The third sensitivity analysis was performed for the change from baseline in mTSS using the ANCOVA with linear extrapolation. The secondary and third sensitivity analyses were applied to the ACR 20 response using the Wald test and logistic regression.

### Safety Analyses

Adverse events for each treatment group were defined by the Medical Dictionary for Regulatory Activities (MedDRA) and presented by system organ class (SOC), higher level term (HLT), and preferred term (PT). The frequency of AEs was displayed as number of subjects experiencing the AEs, percentage of subjects experiencing AEs, and number of AEs. Data were corrected for exposure and reported by 100 patient-years. Laboratory and vital signs evaluation were analyzed over time in the SS for observed cases and end of treatment (LOCF).

The method for safety analyses are further discussed in Section 7.1 Methods.

### Handling of Dropouts or Missing Data:

- ACR 20 response (primary endpoint)  
Subjects, who withdrew for any reason or placebo subjects who escaped, were considered as nonresponders from the time that they dropped out or when escape therapy was initiated. Subjects with missing data at a visit were considered as a nonresponder for that respective visit.
- Change from baseline in the mTSS at Week 24  
Subjects, who have baseline x-rays, who withdrew before Week 24, and who have radiographs taken before their early withdrawal, were included in the analysis by linear extrapolation from the last 2 radiographs before Week 24. Linear extrapolation was also applied for subjects with a missing 24-week measurement. For placebo subjects who escaped early, the last 2 scores before receiving CZP was utilized. The visits utilized for extrapolation included visits at baseline, Week 12, and early withdrawal.

- Change from baseline in the mTSS at Week 48

In general, all missing data (change from baseline) were linearly extrapolated. Therefore, for placebo subjects, all radiographic scores at Week 48 were imputed by using the last 2 mTSS values before CZP treatment. For placebo subjects who switched to one of the CZP groups, the 24-week CZP measurement (for early escape subjects) and the 48-week CZP measurement (for cross over subjects) were imputed. The baseline, Week 12, and Week 24 visits were used for extrapolation. This is a conservative approach that underestimated the difference between placebo and CZP at Weeks 24 and 48.

- HAQ-DI

The Last Observation Carried Forward (LOCF) approach was applied for missing post-baseline values. For placebo subjects who early escaped, LOCF was applied from the time that escape therapy was initiated.

- PASI75 response

Subjects, who withdrew for any reason, were considered nonresponders from the time of drop-out. Subjects, who have missing data at any visit, were counted as nonresponders for that visit. For placebo subjects who early escaped, Week-12 response was used from the time escape therapy was initiated.

Handling of Multiplicity:

A hierarchal test procedure was applied to protect the overall significance level for multiplicity of dose groups and endpoints. For the primary and key secondary endpoints, a predefined order of hypotheses testing, each at a 2-sided 5% alpha level versus placebo, was performed. Depending whether the first test was significant, the second hypothesis was tested with the same alpha level of 5%. Statistical testing for the subsequent hypotheses was performed only if the previous null hypothesis in the hierarchy was rejected.

- (1) ACR 20 response at Week 12 for CZP 200mg every 2 weeks
- (2) ACR 20 response at Week 12 for CZP 400mg every 4 weeks
- (3) ACR 20 response at Week 24 for CZP 200mg every 2 weeks
- (4) ACR 20 response at Week 24 for CZP 400mg every 4 weeks
- (5) Change from baseline in HAQ-DI at Week 24 for CZP 200mg every 2 weeks and CZP 400mg every 4 weeks combined
- (6) Change from baseline in mTSS at Week 24 for CZP 200mg every 2 weeks and CZP 400mg every 4 weeks combined
- (7) PASI75 response at Week 24 for CZP 200mg every 2 weeks and CZP 400mg every 4 weeks combined
- (8) Change from baseline in mTSS at Week 48 for CZP 200mg every 2 weeks and CZP 400mg every 4 weeks combined – not performed for the double-blind analysis

### Handling of Protocol Deviations:

Prior to breaking the blind, protocol deviations were assessed as minor or major by a panel, which included the clinical project manager, trial statistician, and other appropriate clinical study team members.

### 5.3.2 Study PSA001 Conduct

#### *Protocol Amendments*

PSA001 was amended three times.

**Amendment #1** occurred on 23 November 2009 and is actually the first version of the protocol reviewed by the FDA. This amendment was made to the original protocol in order to adapt to the most recent scientific developments in the field. Other changes included updated Sponsor study physician information, corrected typographical errors, and clarifications to the text. Some of the more notable global changes included the following:

- The CASPAR criteria were added to the inclusion criteria.
- Leflunomide was added as an allowed DMARD. On the other hand, HCQ and DMARD combinations were now prohibited.
- The effect of CZP on axial involvement in a subgroup of affected subjects (BASDAI  $\geq 4$ ) at baseline was added as a secondary objective.
- Measurement of HLA-B27 at baseline has been included.
- The swollen and tender joint count assessment was changed from 76/78 joints to 66/68 joints.

**Amendment #2** was composed based on FDA feedback to adjust the statistical analysis plan (SAP) for multiple endpoints, to add an additional secondary endpoint to assess the effect of CZP on psoriatic skin lesions, and to change to the Randomized Set for primary efficacy analysis. In addition, the amendment included clarifications of the description of efficacy assessments for dactylitis, enthesitis, and mNAPSI. Within the protocol text, a few minor clarifications, inconsistencies, and typographical errors were made. A few of the global changes are listed below.

- The Full Analysis Set was replaced by the Randomization Set for primary efficacy analyses.
- The SAP was adjusted for multiple endpoints. A hierarchical test procedure was applied to protect the overall significance level of the multiplicity of dose groups and endpoints with a predefined order of hypotheses testing for the following endpoints: ACR 20 response at Week 12 (CZP 200mg q2wk, CZP

400mg q4wk), ACR 20 response at Week 24 (CZP 200mg q2wk, CZP 400mg q4wk), change from baseline in HAQ-DI at Week 24 (combined dose group), change from baseline in mTSS at Week 24 (combined dose group), PASI75 response at Week 24 (combined dose group), change from baseline in mTSS at Week 48 (combined dose groups).

- One of the key secondary variables was changed from HAQ-DI at Weeks 12, 24, and 48 to HAQ-DI at Week 24 only.
- Assessment of subjects with a PGAP rating “clear” or “almost clear” was added as a secondary endpoint to evaluate psoriatic skin lesions.
- Clarification was added to the dactylitis assessment to state that the LDI basic will be performed according to the Healy and Helliwell study (2007) and Helliwell study (2005).
- Clarification was added that the enthesitis assessment should be performed on the elbows, knees, and heels.
- Description of the mNAPSI assessment was modified in accordance to the Cassell article (2007).
- Clarification was added that abatacept was prohibited – within 3 months prior to baseline, as concomitant therapy, and as rescue treatment.
- The cited liver associated enzymes >2x ULN, serum creatinine >ULN, or WBC <3 x 10<sup>9</sup>/L represented examples of clinically significant laboratory abnormalities were added to the Exclusion Criteria.
- Clarification was added that 1 rescreening of subjects with latent TB who could not complete a minimum of 4 weeks of TB therapy within the Screening Period was permitted.
- Clarification was added that, if the Elispot was negative at Screening for subjects with previously negative Elispot test results, it would be repeated at Weeks 48 and 96.

**Amendment #3** was implemented to increase the approximate number of sites participating in this study and the approximate number of subjects who would be screened because of a higher than expected screen failure rate. In addition, updates were made to the Sponsor personnel and their contact information. Administrative changes were also made for internal consistency. Some of the global changes included the following:

- The approximate number of subjects to be screened was increased from 500 to 700.
- The approximate number of sites participating in the study was increased from 100 to 130.
- Based on FDA feedback, all randomized subjects must be used for primary analysis. Therefore, the statement that 375 subjects would be available for primary efficacy analyses was deleted.

*Protocol Violations*

In compliance with ICH E3 guidelines, protocol deviations important for the conduct, efficacy, and safety of the study were delineated during the blinded data review meeting. Table 5 presents the protocol deviations in study PSA001, as classified by prespecified terms. Overall, there was a high number of protocol deviations (75.6% of all subjects). Total numbers of subjects with protocol deviations were slightly higher in the CZP-treated groups as compared to placebo. The occurrence of an important efficacy deviation did not always lead to exclusion from the PPS data set (defined above “Statistics). Protocol deviations that led to exclusion from PPS were important because these were the ones that impacted primary efficacy. Of the 409 subjects in the RS, 115 subjects (28.1%) were excluded from PPS.

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**Table 5. Summary of Important Protocol Deviations**

	PBO (through DB period)  N=77	PBO (early escape to CZP 200mg)  N=30	PBO (early escape to CZP 400mg)  N=29	PBO  N=136	CZP 200mg  N=138	CZP 400mg  N=135
<b>At least 1 important protocol deviation</b>	60 (77.9%) [211]	9 (30.0%) [11]	9 (31.0%) [18]	97 (71.3%) [309]	106 (76.8%) [345]	102 (75.6%) [384]
<b>Exclusion criteria</b>	9 (11.7%) [12]	-	-	14 (10.3%) [22]	24 (17.4%) [32]	27 (20.0%) [35]
<b>Inclusion criteria</b>	2 (2.6%) [4]	-	-	2 (1.5%) [4]	4 (2.9%) [5]	3 (2.2%) [5]
<b>Procedural non-compliance</b>	53 (68.8%) [105]	6 (20.0%) [7]	6 (20.7%) [11]	87 (64.0%) [170]	86 (62.3%) [173]	82 (60.7%) [167]
<b>Prohibited medication/treatment</b>	19 (24.7%) [60]	1 (3.3%) [1]	2 (6.9%) [3]	24 (17.6%) [72]	27 (19.6%) [86]	33 (24.4%) [123]
<b>Study medication compliance</b>	19 (24.7%) [24]	3 (10.0%) [3]	4 (13.8%) [4]	27 (19.9%) [33]	32 (23.2%) [39]	30 (22.2%) [35]
<b>Withdrawal criteria</b>	6 (7.8%) [6]	-	-	8 (5.9%) [8]	8 (5.8%) [10]	18 (13.3%) [19]

Source: PSA001 Tables, Table 1.5, pages 88-91  
 [#] -- number of important violations

## 6 Review of Efficacy

### Efficacy Summary

The clinical efficacy data are derived from one study, PsA001.

The primary endpoint is ACR 20 Response at Week 12. Based on the primary analysis and the multiple sensitivity and secondary analyses, the certolizumab pegol-treated groups show significantly greater proportions of ACR 20

responders than the placebo group. This difference was also seen at Week 24. Numerically, there were more responders in the subjects who received certolizumab 200mg every other week.

As a measure of physical function, subjects on certolizumab pegol also had a significantly greater improvement in HAQ-DI at Week 24. Again, numerically there was a greater change in the CZP 200mg q2w group.

The radiographic outcome results did not demonstrate a significant difference between CZP and the placebo add-on control group by the primary analysis. On review, it appears that the prespecified imputation rules may have led to physiologically unrealistic results. The statistical review team reanalyzed the radiographic results using imputation methods that have been previously used (linear extrapolation) or that have face validity (i.e., using observed data for all patients, including those who had crossed over to other treatment, rather than counting those data as missing). Using these analyses, the radiographic data at Week 24 supported a conclusion of a treatment benefit associated with CZP, statistically significantly less progression in mTSS scores in the CZP 200mg q2w group than in the placebo group, and a trend toward less progression in the CZP 400mg q4w group.

Lastly, assessment of PASI75 was used as a measure of skin response. Once again, there were more PASI75 responders in the CZP-treated groups than in the placebo group. Also, like the other endpoints, there were numerically more responders in the subjects who received certolizumab pegol 200mg. It is

(b) (4)

In conclusion, the results of PsA001 support the efficacy of certolizumab pegol in the treatment of active PsA. Certolizumab pegol has a favorable treatment effect on signs and symptoms as well as physical function. The 200 mg q2w regimen of Certolizumab pegol appeared to have a numerically greater improvement than the 400 mg q4w regimen for the primary and key secondary endpoints, including radiographic outcome. Thus, the data suggest the 200 mg q2w regimen may be preferable, and the dosing recommendation in PsA should be consistent with the RA dosing recommendation; specifically, loading with 400mg at Weeks 0, 2, 4 followed by 200mg every 2 weeks. Maintenance with 400mg every 4 weeks can be considered as an alternative.

## 6.1 Indication

UCB, Inc. proposes that certolizumab pegol be indicated for the treatment of adult patients with active psoriatic arthritis. This indication would add to the

already approved indications of (1) 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 and (2) treatment of adults with moderately to severely active rheumatoid arthritis.

### 6.1.1 Methods

Clinical efficacy data to provide evidence for regulatory approval of the proposed indication was derived from a single study, PsA001. The study enrolled patients with active PsA. The study design, efficacy endpoints, and analyses were discussed in detail in Section 5.3 (Discussion of Individual Studies/Clinical Trials).

In brief, the Randomized Set was prespecified as the primary analysis set for efficacy. UCB indicates that two main objectives were, after administration of CZP, assessment of (1) signs and symptoms of active PsA and (2) inhibition of progression of structural damage. However, based on the predefined order of hypotheses testing, ACR 20 response at Week 12 is the primary endpoint. Change from baseline in mTSS at Week 24 falls much later in the hierarchy, so it should be considered a key secondary endpoint along with change from baseline in HAQ-DI at Week 24 and PASI75 response at Week 24.

### 6.1.2 Demographics

Approximately 400 subjects with active PsA comprise the study population in the Phase 3 PsA study, PsA001. The treatment arms enrolled patients with generally comparable demographic characteristics, as presented in Table 6. There was a very slight female predominance, and the majority of subjects were Caucasian. Most of the subjects also had an elevated BMI.

Table 7 presents the baseline disease characteristics in the subjects enrolled in PsA001. The subjects' baseline disease was very similar across treatment arms in all categories. As fulfilling CASPAR criteria was one of the inclusion criteria, nearly all subjects in all the treatment arms had a score of  $\geq 3$ . Interestingly, the majority of subjects (over 80% in each treatment arm) also had axial involvement. This is a little higher than the general PsA population in whom the frequency of spondylitis/sacroiliitis is generally estimated between 5-36% (Cantini et al., 2010). Not all components of the ACR response (such as the PAAP, PtGADA, PhGADA) were calculated at baseline. However, the other components (swollen/tender joint count, HAQ-DI, and inflammatory markers) were quite comparable across treatment arms. In addition, the majority of subjects had concomitant skin disease with greater than 50% in each group

having  $\geq 3\%$  skin involvement. Lastly, approximately 1/3 of subjects in each treatment arm had dactylitis; approximately 60% had enthesitis; approximately 70% had nail involvement.

Table 8 presents both prior and baseline medications for subjects in PsA001. In general, nearly all the subjects were previously treated with DMARDs; this was the case for all treatment arms. However, the exact DMARD differed slightly with only the previous use of MTX being similar. The number of subjects treated with steroids was similar in all three treatment arms. A higher proportion of subjects in the CZP 400mg q4w group were treated with NSAIDs. Like DMARDs, the overall history of biologic use was similar across treatment arms, but there were slightly different numbers for the specific biologic used.

For concomitant medications, on the other hand, the proportions for all PsA medications (steroids, NSAIDs, DMARDs – including the specific DMARD) are similar across treatment arms.

**Table 6. Baseline Demographics in Phase 3 PsA study**

Baseline Demographic Characteristics, subjects in PsA001 (ITT)				
		PBO	CZP	
			200mg	400mg
Subjects		136	138	135
Gender, n (%)	Female	79 (58.1%)	74 (53.6%)	73 (54.1%)
	Male	57 (41.9%)	64 (46.4%)	62 (45.9%)
Age, years	Mean (SD)	47.3 (11.1)	48.2 (12.3)	47.1 (10.8)
Race, n (%)	White	132 (97.1%)	135 (97.8%)	133 (98.5%)
	Black	0	1 (0.7%)	1 (0.7%)
	Asian	1 (0.7%)	0	0
	American Indian/Alaskan Native	1 (0.7%)	1 (0.7%)	0
	Other	2 (1.5%)	1 (0.7%)	1 (0.7%)
Height, cm	Mean (SD)	168.18 (10.24)	167.91 (9.98)	169.56 (8.48)
Weight, kg	Mean (SD)	82.63 (19.94)	85.80 (17.65)	84.83 (18.68)
BMI, kg.m2	Mean (SD)	29.18 (6.72)	30.50 (6.190)	29.56 (6.55)

Source: PsA001 Wk 24 CSR, Table 2.1.1, page 129-131

**Table 7. Baseline Disease Severity in Phase 3 PsA Study**

<b>Baseline disease severity characteristics of subjects in PSA001 (ITT)</b>			
	PBO	CZP	
		200 mg	400 mg
Subjects Randomized	136	138	135
<b>Joint-related disease characteristics</b>			
<b>PsA subtypes, n(%)</b>			
CASPAR criteria fulfilled (score≥3)	134 (98.5%)	137 (99.3%)	133 (98.5%)
Axial involvement	114 (83.8%)	119 (86.2%)	114 (84.4%)
PsA duration (years), Mean ± SD	7.91±7.67	9.62±8.50	8.11±8.30
<b>ACR core components, Mean±SD</b>			
Number of swollen joints (0-66)	10.43	11.04	10.48
Number of tender joints (0-66)	19.90	21.51	19.55
Patient assessment of pain (VAS, 0-10cm)			
Patient global assessment of disease (VAS, 0-10cm)			
Physician's global assessment of disease (VAS, 0-10cm)			
HAQ disability index (0-3)	1.30	1.33	1.29
CRP (mg/L)	18.56±25.46	15.36±27.78	13.71±14.33
ESR (mm/h)	41.5±19.7	41.7±19.7	38.5±20.1
DAS-28	4.99	5.04	4.99
<b>Soft-tissue disease characteristics</b>			
Subjects with dactylitis, n (%)	45 (33.1%)	47 (34.1%)	47 (34.8%)
Subjects with enthesitis, n (%)	91 (66.9%)	88 (63.8%)	84 (62.2%)
Subjects with nail findings, n (%)	103 (75.7%)	92 (66.7%)	105 (77.8%)
<b>Skin-related disease characteristics</b>			
Current psoriasis	128 (94.1%)	130 (94.2%)	124 (91.9%)
Personal history of psoriasis	129 (94.9%)	131 (94.9%)	127 (94.1%)
Family history of psoriasis	52 (38.2%)	45 (32.6%)	51 (37.8%)
Subjects with ≥3% BSA skin involvement, n (%)	86 (63.2%)	90 (65.2%)	76 (56.3%)

Sources: PsA001 Wk 24 CSR, Table 2.3.1, page 139; Table 2.4.1, page 145; Table 2.6.1, page 151-157

**Table 8. Summary of Prior and Baseline Medications**

<b>Summary of Prior and Baseline Medications for Psoriatic Arthritis in randomized patients</b>			
	<b>PSA001</b>		
	<b>PBO</b>	<b>CZP</b>	
		<b>200 mg</b>	<b>400mg</b>
Subjects Randomized	136	138	135
<b>Prior Medications, n (%)</b>			
<b>Any DMARD</b>	134 (98.5)	134 (97.1)	132 (97.8)
Methotrexate	124 (91.1)	124 (89.8)	122 (90.4)
Leflunomide	10 (7.4)	11 (8.0)	22 (16.3)
Sulfasalazine	37 (27.2)	47 (34.1)	28 (20.7)
Cyclosporine	16 (11.8)	13 (9.4)	10 (7.4)
Azathioprine	1 (0.7)	-	1 (0.7)
Hydroxychloroquine	6 (4.4)	7 (5.0)	4 (2.9)
Gold preparations	5 (3.7)	3 (2.2)	5 (3.7)
Cyclophosphamide	1 (0.7)	-	-
<b>Steroids</b>	38 (27.9)	39 (28.3)	34 (25.2)
<b>NSAIDs</b>	114 (83.8)	113 (81.9)	123 (91.1)
<b>Past Anti-TNF<math>\alpha</math> inhibitors and biologics</b>	28 (20.6)	33 (23.9)	25 (18.5)
Adalimumab	13 (9.6)	10 (7.2)	10 (7.4)
Etanercept	9 (6.6)	15 (10.9)	8 (5.9)
Infliximab	2 (1.5)	5 (3.6)	5 (3.7)
Golimumab	2 (1.5)	1 (0.7)	1 (0.7)
Abatacept	3 (2.2)	2 (1.4)	3 (2.2)
Ustekinumab	1 (0.7)	-	-
<b>Concomitant/Baseline Medications, n (%)</b>			
<b>Steroids</b>	24 (31.2)	4 (13.3)	5 (17.2)
<b>NSAIDs</b>	57 (74.0)	23 (76.6)	19 (65.5)
<b>Any DMARD</b>	101 (74.8)	201 (73.6)	238 (71.7)
Methotrexate	88 (65.2)	176 (64.5)	213 (64.2)
Leflunomide	8 (5.9)	12 (4.4)	12 (3.6)
Sulfasalazine	4 (3.0)	12 (4.4)	12 (3.6)

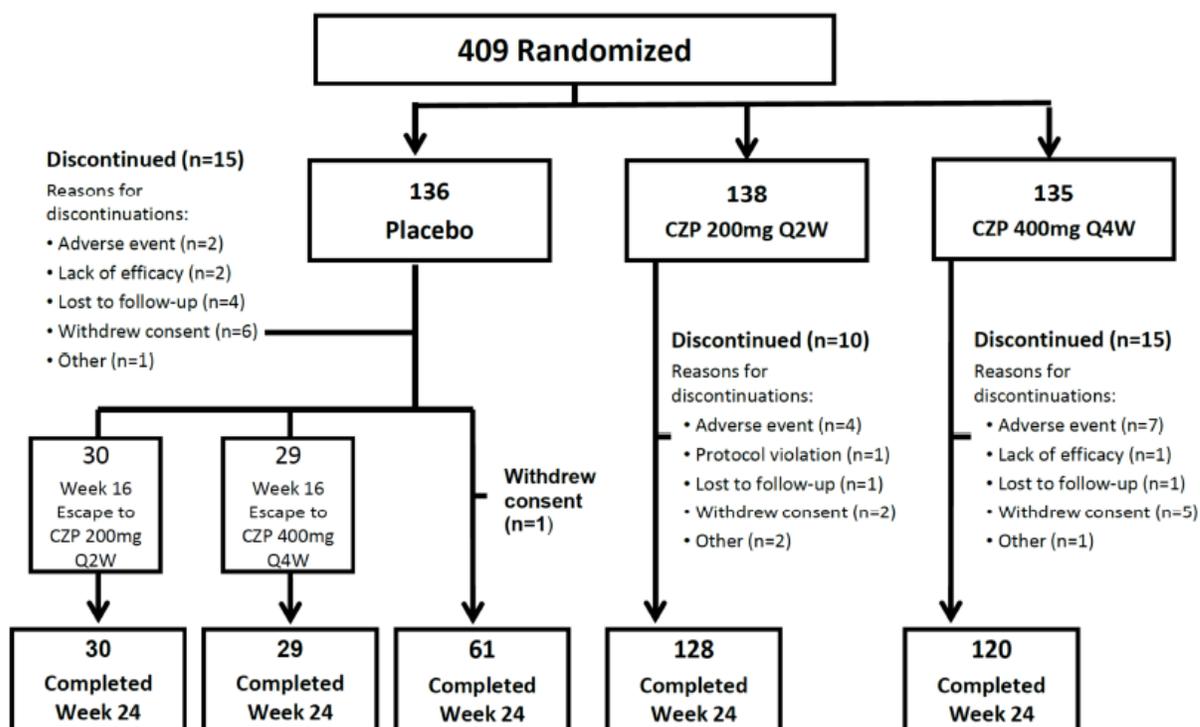
Source: PSA001 Wk24 CSR, Table 2.11.1, page 234-; Table 2.12.1, page 240; Table 2.10.1, page 232; Table 2.14.1, page 276; Table 2.15.1, page 280; Table 2.16.1, page 310

### 6.1.3 Subject Disposition

Figure 2 displays the patient disposition through the 24-week Double-Blind Treatment Period. Six-hundred three subjects were screened, but 409 were eligible for randomization. The number of subjects who discontinued the study drug was similar across treatment arms, and the most common reasons for discontinuation were adverse event and consent withdrawal.

Fifty-nine subjects in the placebo group met escape criteria at Week 16 and were randomized to one of the CZP dose groups (30 to CZP 200mg and 29 to CZP 400mg). After an Information Request (IR) was placed by the Statistics Team, UCB provided information on the number of subjects in the CZP groups who met escape criteria but did not have the opportunity to escape based on the study design. A total of 18 subjects in the CZP 200mg group and 21 subjects in the CZP 400mg met escape criteria.

**Figure 2. Flowchart of Subject Disposition**



CZP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks  
 Data sources: PsA001 Week 24 CSR [Table 1.1](#), [Table 1.3](#), [Table 1.4](#)  
 Source: Summary of Clinical Efficacy, Fig.2-2, page 52.

#### 6.1.4 Analysis of Primary Endpoint(s)

Although the primary endpoint was technically the proportion of ACR20 responders at Week 12, this section will include data for the secondary endpoints and sensitivity analyses pertaining to ACR responses. Table 9 displays the ACR 20 responders in all treatment arms at Weeks 12 and 24. As shown in Table 9, there is a statistically significant difference between the two CZP-treated groups and placebo at Week 12 and 24. It should be noted that, for CZP 400mg, the difference from placebo is numerically smaller for both endpoints.

**Table 9. ACR 20 Responders at Weeks 12 and 24 (RS, with imputation)**

	<b>PBO N=136</b>	<b>CZP 200mg q2wk N=138</b>	<b>CZP 400mg q4wk N=135</b>
<b>Week 12</b>			
<b>Responders (%)</b>	24.3	58.0	51.9
<b>95% CI</b>	(17.1, 31.5)	(49.7, 66.2)	(43.4, 60.3)
<b>Difference to PBO (%)</b>	-	33.7	27.6
<b>95% CI</b>	-	(22.8, 44.6)	(16.5, 38.7)
<b>p-value</b>	-	<0.001	<0.001
<b>Week 24</b>			
<b>Responders (%)</b>	23.5	63.8	56.3
<b>95% CI</b>	(16.4, 30.7)	(55.7, 71.8)	(47.9, 64.7)
<b>Difference to PBO (%)</b>	-	40.2	32.8
<b>95% CI</b>	-	(29.5, 51.0)	(21.8, 43.8)
<b>p-value</b>	-	<0.001	<0.001

Randomized Set (RS), with imputation

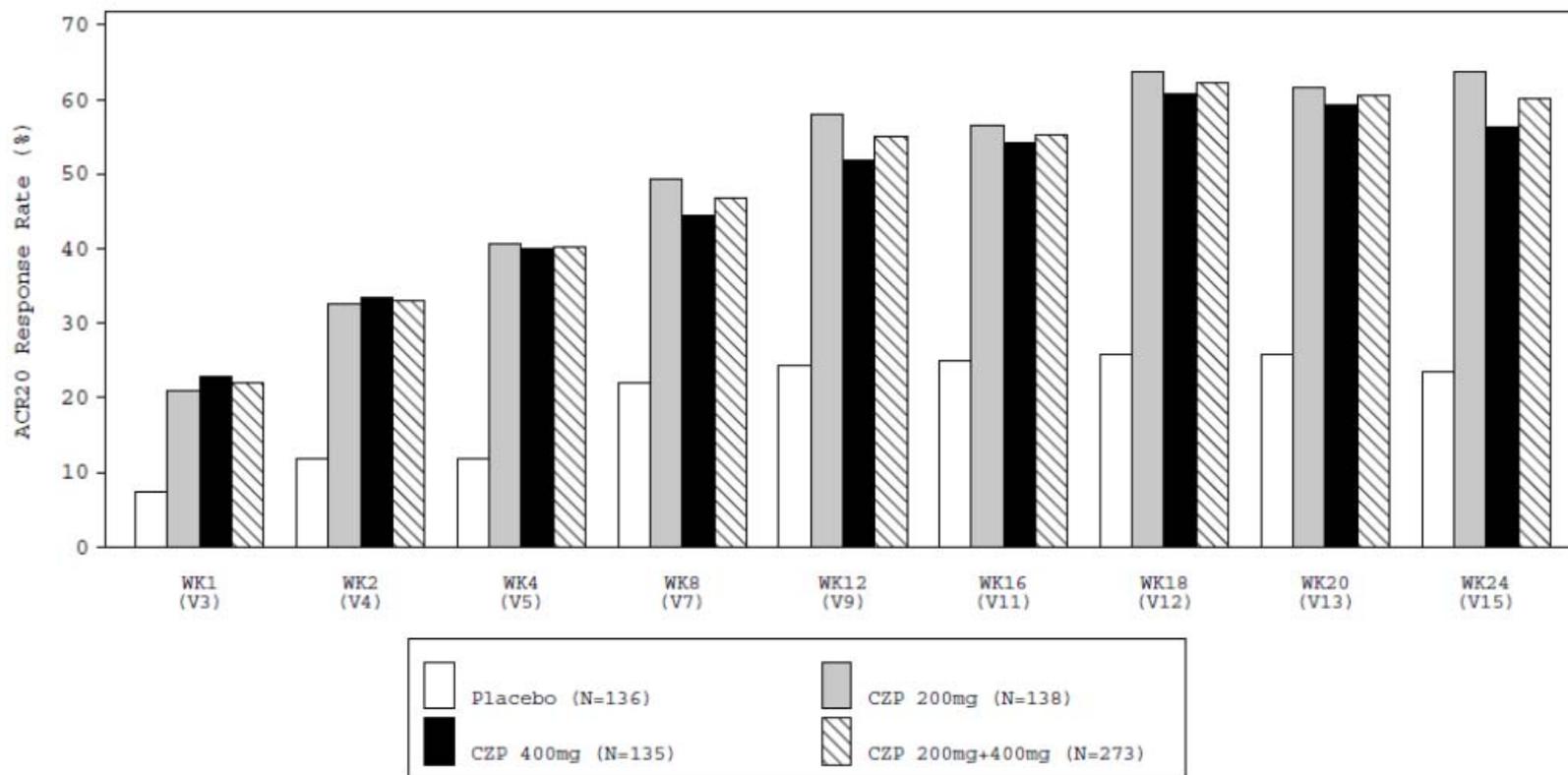
NonResponder Imputation – subjects who withdrew for any reason or PBO who early escaped were considered nonresponders from the time that they dropped out or escaped. Subjects who had missing data at a visit were considered nonresponders for that visit.

Source: Summary of Clinical Efficacy, Tables 2-10, 2-11, pages 54,56.

UCB further confirmed the ACR 20 findings by performing several sensitivity analyses. They looked at ACR 20 response in the different data sets – e.g., the Full Analysis Set (excluding those with missing data), the Per-Protocol Set (excluding those with missing data and protocol deviations), and the Completer Set (using only observed data, without imputations). In addition, the analyses were performed using the Wald test (as displayed in Table 9) and logistic regression. With all of these different analyses, similar results were obtained. The difference in ACR 20 response at Week 12 in subjects treated with CZP 200mg and 400mg was significantly different from placebo.

Figure 3 shows the ACR 20 responses for each treatment arm at each visit through Week 24. This figure shows that there is a greater response in the CZP-treated groups at every time point. The ACR 20 response appears to reach a plateau in the CZP-treated groups around Week 18 or 20. Lastly, what is notable is that the proportion of ACR 20 responders in the CZP 200mg group is greater than that in the CZP 400mg group at every visit after Week 4, although the difference is small.

Figure 3. ACR 20 Response Over Time



Source: Summary of Clinical Efficacy, Figure 2-4, page 59.

The component variables of the ACR response criteria include swollen and tender joint counts, HAQ-DI, patient's assessment of arthritis pain (PAAP), patient's global assessment of disease activity (PtGADA), physician's global assessment of disease activity (PhGADA), and CRP. CZP treatment was associated with improvement in all of these components. Table 10 shows the mean, the mean change from baseline, and the difference of the mean change from placebo, for each of the ACR components.

**Table 10. ACR Components at Week 12**

	<b>PBO<sup>a</sup></b>	<b>CZP 200mg q2wks</b>	<b>CZP 400mg q4wks</b>
	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>
<b>Week 12</b>			
<b>Swollen joint count</b>			
<b>Baseline, mean (SD)</b>	10.43 (7.64)	11.04 (8.83)	10.48 (7.47)
<b>Week 12, mean (SD)</b>	8.70 (10.49)	4.08 (5.94)	4.74 (6.73)
<b>Week 12, mean change from baseline (SD)</b>	-1.73 (8.75)	-6.96 (7.94)	-5.73 (6.10)
<b>Week 12, difference from PBO<sup>b</sup></b>			
<b>LS mean (SE)</b>	-	-5.01 (0.81)	-4.01 (0.81)
<b>95% CI</b>	-	-6.60, -3.42	-5.60, -2.41
<b>p-value</b>	-	<0.001	<0.001
<b>Tender joint count</b>			
<b>Baseline, mean (SD)</b>	19.90 (14.65)	21.51 (15.28)	19.55 (14.77)
<b>Week 12, mean (SD)</b>	16.45 (14.19)	11.16 (14.95)	11.22 (14.25)
<b>Week 12, mean change from baseline (SD)</b>	-3.45 (11.60)	-10.35 (13.74)	-8.33 (14.06)
<b>Week 12, difference from PBO<sup>b</sup></b>			
<b>LS mean (SE)</b>	-	-6.31 (1.40)	-4.94 (1.41)
<b>95% CI</b>	-	-9.07, -3.55	-7.71, -2.17
<b>p-value</b>	-	<0.001	<0.001
<b>HAQ-DI</b>			
<b>Baseline, mean (SD)</b>	1.30 (0.66)	1.33 (0.66)	1.29 (0.60)
<b>Week 12, mean (SD)</b>	1.15 (0.67)	0.87 (0.74)	0.90 (0.67)
<b>Week 12, mean change from baseline (SD)</b>	-0.16 (0.36)	-0.45 (0.56)	-0.39 (0.47)
<b>Week 12, difference from PBO<sup>b</sup></b>			
<b>LS mean (SE)</b>	-	-0.30 (0.06)	-0.24 (0.06)
<b>95% CI</b>	-	-0.40, -0.19	-0.35, -0.13
<b>p-value</b>	-	<0.001	<0.001
<b>PAAP</b>			
<b>Baseline, mean (SD)</b>	60.0 (22.0)	59.7 (20.7)	61.1 (18.5)
<b>Week 12, mean (SD)</b>	50.2 (23.7)	32.8 (25.2)	38.6 (25.9)
<b>Week 12, mean change from baseline (SD)</b>	-9.9 (21.0)	-26.9 (28.7)	-22.5 (23.4)
<b>Week 12, difference from PBO<sup>b</sup></b>			
<b>LS mean (SE)</b>	-	-17.2 (2.7)	-12.1 (2.7)
<b>95% CI</b>	-	-22.6, -11.9	-17.4, -6.7
<b>p-value</b>	-	<0.001	<0.001
<b>PtGADA-VAS</b>			
<b>Baseline, mean (SD)</b>	57.0 (22.4)	60.2 (21.0)	60.2 (18.4)
<b>Week 12, mean (SD)</b>	50.2 (23.9)	32.6 (24.5)	39.6 (25.5)
<b>Week 12, mean change from baseline (SD)</b>	-6.8 (22.3)	-27.6 (28.3)	-20.7 (25.1)

<b>Week 12, difference from PBO<sup>b</sup></b>			
<b>LS mean (SE)</b>	-	-19.1 (2.7)	-12.1 (2.7)
<b>95% CI</b>	-	-24.4, -13.7	-17.5, -6.7
<b>p-value</b>	-	<0.001	<0.001
<b>PhGADA-VAS</b>			
<b>Baseline, mean (SD)</b>	58.7 (18.7)	56.8 (18.2)	58.2 (18.9)
<b>Week 12, mean (SD)</b>	44.1 (23.8)	24.8 (28.7)	26.7 (20.7)
<b>Week 12, mean change from baseline (SD)</b>	-14.6 (20.8)	-32.0 (22.2)	-29.5 (21.1)
<b>Week 12, difference from PBO<sup>b</sup></b>			
<b>LS mean (SE)</b>	-	-18.5 (2.3)	-15.0 (2.3)
<b>95% CI</b>	-	-23.0, -13.9	-19.6, -10.4
<b>p-value</b>	-	<0.001	<0.001
<b>CRP (mg/L)</b>			
<b>Baseline, mean (SD)</b>	18.56 (25.46)	15.36 (27.78)	13.71 (14.33)
<b>Week 12, mean (SD)</b>	14.75 (20.55)	5.67 (8.23)	6.34 (11.30)
<b>Week 12, mean change from baseline (SD)</b>	-3.81 (13.91)	-9.70 (28.26)	-7.37 (15.69)
<b>Week 12, difference from PBO<sup>b</sup></b>			
<b>LS mean (SE)</b>	-	-8.03 (1.51)	-6.83 (1.52)
<b>95% CI</b>	-	-11.00, -5.07	-9.81, -3.85
<b>p-value</b>	-	<0.001	<0.001

Randomized Set, with Imputation

a For the entire PBO group, last observation prior to escape was carried forward for subjects escaping to CZP

b ANCOVA model with treatment, region, and prior anti-TNF $\alpha$  exposure (yes/no) as factors and baseline score as covariate

Source: Summary of Clinical Efficacy, Table 2-13, pages 62-65

PSA001 24-week CSR Tables, Table 4.22.1, pages 531, 536; Table 4.25.1, pages 565, 570; Table 4.26.1, pages 591,596; Table 4.27.1, pages 617, 622; Table 4.28.1, pages 643, 648; Table 4.29.1, pages 669, 674; Table 4.30.1, pages 693, 697.

Although these are secondary endpoints, for completeness, the proportion of ACR 50 and ACR 70 responders is summarized here (Table 11). Both ACR 50 and ACR 70 responses were consistent with the pattern observed with ACR 20. There was a statistically significant difference from placebo for both CZP 200mg and CZP 400mg. Again, the numerical difference was smaller for CZP 400mg than for CZP 200mg.

Overall, these results demonstrate statistically significant improvement in signs and symptoms for both doses of CZP. Numerically, the improvement appears to be greater for CZP 200mg q2w than for CZP 400mg q4w.

**Table 11. ACR 50 and ACR 70 Responders at Weeks 12 and 24**

	<b>PBO N=136</b>	<b>CZP 200mg q2wk N=138</b>	<b>CZP 400mg q4wk N=135</b>
<b>ACR 50</b>			
<b>Week 12</b>			
<b>Responders (%)</b>	11.0	36.2	32.6
<b>Difference to PBO (%)</b>	-	25.2	21.6
<b>95% CI</b>		(15.6, 34.8)	(12.1, 31.1)
<b>p-value</b>	-	<0.001	<0.001
<b>Week 24</b>			
<b>Responders (%)</b>	12.5	44.2	40.0
<b>Difference to PBO (%)</b>	-	31.7	27.5
<b>95% CI</b>		(21.7, 41.7)	(17.5, 37.5)
<b>p-value</b>	-	<0.001	<0.001
<b>ACR 70</b>			
<b>Week 12</b>			
<b>Responders (%)</b>	2.9	24.6	12.6
<b>Difference to PBO (%)</b>	-	21.7	9.7
<b>95% CI</b>		(14.0, 29.4)	(3.4, 15.9)
<b>p-value</b>	-	<0.001	0.003
<b>Week 24</b>			
<b>Responders (%)</b>	4.4	28.3	23.7
<b>Difference to PBO (%)</b>	-	23.8	19.3
<b>95% CI</b>		(15.6, 32.1)	(11.3, 27.3)
<b>p-value</b>	-	<0.001	<0.001

Randomized Set (RS), with imputation

NonResponder Imputation – subjects who withdrew for any reason or PBO who early escaped were considered nonresponders from the time that they dropped out or escaped. Subjects who had missing data at a visit were considered nonresponders for that visit.

Source: PSA001 24-week CSR Tables, Table 4.8.1, page 418, 420.

### 6.1.5 Analysis of Secondary Endpoint(s)

#### HAQ-DI

After the endpoints of ACR 20 at Week 12 and 24 on the prespecified hierarchy, the next key secondary endpoint is change from baseline in HAQ-DI. UCB's endpoint was actually analysis of HAQ-DI in the combined dose group (i.e., all CZP-treated subjects). However, it is more informative to review the 2 doses separately.

Table 12 displays the change from baseline in HAQ-DI at Week 24 for all treatment arms and for the combined CZP group. There was a decrease in HAQ-DI from baseline in all treatment arms. As defined in Appendix 9.5, a higher score is reflective of more severe disability; thus, a decrease in HAQ-DI is reflective of improvement. The difference of this change from placebo for both CZP doses is statistically significant. Like the ACR responses already reviewed, the difference is numerically greater for CZP 200mg than for CZP 400mg.

**Table 12. Change from Baseline in HAQ-DI at Week 24**

Week 24	PBO <sup>a</sup> N=136	CZP 200mg q2wks N=138	CZP 400mg q4wks N=135	CZP 200mg q2w + CZP 400mg q4w N=273
<b>Change from Baseline</b>				
LS mean (SE) <sup>b</sup>	-0.19 (0.05)	-0.54 (0.05)	-0.46 (0.05)	-0.50 (0.04)
95% CI <sup>b</sup>	-0.29, -0.09	-0.64, -0.44	-0.56, -0.36	-0.58, -0.42
<b>Difference from PBO</b>				
LS mean (SE) <sup>b</sup>	-	-0.35 (0.06)	-0.26 (0.06)	-0.31 (0.06)
95% CI <sup>b</sup>	-	-0.47, -0.22	-0.39, -0.14	-0.42, -0.20
p-value <sup>b</sup>	-	<0.001	<0.001	<0.001

Randomized Set, with Imputation

a For the entire PBO group, last observation prior to escape was carried forward to Week 24 for subjects escaping to CZP

b Analysis of covariance (ANCOVA) model with treatment, region, and prior anti-TNF $\alpha$  exposure (yes/no) as factors and Baseline score as a covariate

Source: Summary of Clinical Efficacy, Table 2-12, page 57.

The minimal clinically important difference (MCID) in change in HAQ-DI is 0.3 points (Mease et al., 2005). Thus, any subject with  $\geq 0.3$  change in HAQ-DI was used to define a HAQ-DI responder. Table 13 shows the HAQ-DI responders at Weeks 12 and 24. There are significantly more responders in the CZP-treated groups than in the placebo-treated group at both Weeks 12 and 24. The number of responders is numerically higher in CZP 400mg at Week 12 but minimally lower at Week 24. Thus, there does not appear to be a consistent difference between the two CZP dose regimens.

**Table 13. HAQ-DI Responders at Weeks 12 and 24**

MCID $\geq 0.3$ points <sup>1</sup>	PBO <sup>a</sup> N=136	CZP 200mg q2wks N=138	CZP 400mg q4wks N=138	CZP 200mg q2w + CZP 400mg q4w N=273
<b>Week 12</b>				
Responders, n (%)	29 (21.3)	63 (45.7)	66 (48.9)	129 (47.3)
Difference from PBO, % (95% CI)	-	24.3 (13.5, 35.1)	27.6 (16.7, 38.5)	25.9 (16.8, 35.0)
p-value	-	<0.001	<0.001	<0.001
<b>Week 24</b>				
Responders, n (%)	21 (15.4)	68 (49.3)	65 (48.1)	133 (48.7)
Difference from PBO, % (95% CI)	-	33.8 (23.5, 44.2)	32.7 (22.3, 43.1)	33.3 (24.8, 41.8)
p-value	-	<0.001	<0.001	<0.001

Randomized Set, with Imputation

<sup>1</sup> Meese et al., 2005

a For the entire placebo group, nonresponder imputations (NRI) was used for subjects escaping to CZP

Source: Summary of Clinical Efficacy, Table 2-14, page 67.

### Radiographic Inhibition

Change from baseline in mTSS at Week 24 is the next endpoint on the prespecified hierarchy. Based on UCB's pre-specified imputation strategy, linear extrapolation was used where possible for missing data. Therefore, for subjects with baseline x-rays who withdrew before Week 24 or who have missing Week 24 measurements, linear extrapolation was used based on the mTSS scores from the last 2 measurements before Week 24. For placebo subjects who entered early escape, the last 2 scores before receiving CZP were utilized. For subjects with only 1 or no radiographs, 0 was used for Baseline mTSS, and 365.5 was used for Week 24. These numbers were chosen because 0 was the lowest Baseline value observed in the entire randomized population and 365.5 was the highest Week 24 value observed. The statistical review by Kiya Hamilton, PhD, (primary statistics reviewer) details the prespecified rules for imputation.

Table 14 presents the change from baseline in mTSS at Week 24 based on the pre-specified analysis. With this analysis, there appears to be a worsening from baseline in all the treatment arms, and subjects who received placebo did worse than subjects treated with CZP. However, the difference in the change was not statistically significant for any of the doses.

**Table 14. Change from Baseline in mTSS at Week 24 - Sponsor's Pre-Specified Analysis**

	PBO <sup>a</sup>	CZP 200mg q2wks	CZP 400mg q4wks	CZP 200mg q2w + CZP 400mg q4w
	N=136	N=138	N=135	N=273
<b>Week 24, mean change from baseline (SE)</b>	28.92 (7.73)	11.52 (7.59)	25.05 (7.92)	18.28 (6.07)
<b>Week 24, difference from PBO<sup>b</sup></b>				
<b>LS mean (SE)</b>	-	-17.40 (9.63)	-3.88 (9.65)	-10.64 (8.35)
<b>95% CI</b>	-	(-36.32, 1.52)	(-22.86, 15.10)	(-27.05, 5.77)
<b>p-value</b>	-	0.071	0.688	0.203

a For the entire PBO group, linear extrapolation was used for subjects escaping to CZP

b ANCOVA model with treatment, region, and prior anti-TNFα exposure (yes/no) as factors and baseline score as covariate  
 Source: PSA001 Week 24 CSR Table 4.9.1, page 426.

There were a total of 81 missing values. Fifty-six subjects had missing values from 1 or more visits – 35 subjects 1 visit, 17 subjects 2 visits, and 4 subjects all 3 visits.

UCB argues that the results from the pre-specified analysis are not physiologically possible. UCB refers to the mean change from baseline that was seen with other anti-TNFα medications to state that the results in Table 14 are not consistent with what is known about TNFα inhibition.

#### Week 24 data

- Etanercept – 1.0 (placebo) vs. -0.03 (study drug)

- Infiximab – 0.82 (placebo) vs. -0.7 (study drug)
- Adalimumab – 1.0 (placebo) vs. -0.2 (study drug)
- Golilumab – 0.27 (placebo) vs. -0.16 (study drug)

Thus, in an attempt to obtain more “realistic” data, UCB re-analyzed the radiographic data in a number of ways. Table 15 describes how different missing data situations were handled using the pre-specified analysis and the new post-hoc analysis.

**Table 15. mTSS Cases for Imputation (Pre-defined and Post-Hoc Rules)**

	Baseline	Week 12	Week 24
<b>Case 1 (n=4)</b>	Missing	Missing	Missing
SAP	Minimum value observed (0)	Linear interpolation	Maximum value observed (356.5)
Post-hoc analysis	Median change from Baseline for entire study population (0)		
<b>Case 2 (n=5)</b>	Missing	Available	Available
SAP	Linear extrapolation	Actual Week 12	Actual Week 24
Post-hoc analysis	No change		
<b>Case 3 (n=16)</b>	Available	Missing	Missing
SAP	Actual Baseline	Linear interpolation	Maximum value observed (356.5)
Post-hoc analysis	Median change from Baseline for entire study population (0)		
<b>Case 4 (n=7)</b>	Available	Missing	Available
SAP	Actual Baseline	Linear interpolation	Actual Week 24
Post-hoc analysis	No change		
<b>Case 5 (n=1)</b>	Missing	Available	Missing
SAP	Minimum value observed (0)	Actual Week 12	Maximum value observed (356.5)
Post-hoc analysis	Median change from Baseline for entire study population (0)		
<b>Case 6 (n=23)</b>	Available	Available	Missing
SAP	Actual Baseline	Actual Week 12	Linear extrapolation from Baseline and Week 12
Post-hoc analysis	No change		
<b>Case 7 (n=0)</b>	Missing	Missing	Available
SAP	Minimum value observed (0)	Linear interpolation	Actual Week 24
Post-hoc analysis	Median change from Baseline for entire study population (0)		
<b>Case 8 (n=353)</b>	Available	Available	Available
SAP	Actual Baseline	Actual Week 12	Actual Week 24
Post-hoc analysis	No change		

Source: PSA001 Clinical Study Report, Table 6-3, page 106.

Table 16 briefly presents some of the Sponsor’s sensitivity and post-hoc analyses of the radiographic data. For example, the Sponsor did use a retrieved drop-out approach to analyzing the data for the placebo subjects who early escaped. Linear extrapolation (as described for the pre-specified analysis) was performed for the other missing data. The results looked very similar to pre-defined primary analysis. The third analysis is one that only used observed data, i.e., excluding all missing data. These results seem to show a greater treatment effect in CZP-treated subjects, but these results are likely biased given all placebo subjects who entered early escape are not included. Lastly, the fourth analysis in this table is one of UCB’s post-hoc strategies with which linear extrapolation was done using the median change from baseline to Week 24 (instead of the minimum and maximum observed values). In addition, some measurements were excluded (and counted as missing data) if the available radiographs were taken less

than 8 weeks apart. UCB claims that these results are perhaps most reflective of the treatment effect of CZP.

**Table 16. Sponsor's Different Analyses of mTSS Change from Baseline at Week 24**

	Placebo N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mgQ2W+ CZP 400mg Q4W N=273
<b>SAP-predefined primary analysis (Population: RS)</b> Imputation included linear extrapolation and slotting approach without a specified minimum window between radiograph time points. For subjects with 1 or 0 radiographs, 0 was used for Baseline and 365.5 was used for Week 24.				
LS mean (SE)	28.92 (7.73)	11.52 (7.59)	25.05 (7.92)	18.28 (6.07)
<b>SAP-predefined analysis utilizing CZP data for placebo-escape subjects (Population: RS)</b> Imputation included linear extrapolation and slotting approach without a specified minimum window between radiograph time points. For subjects with 1 or 0 radiographs, 0 was used for Baseline and 365.5 was used for Week 24.				
LS mean (SE)	24.87 (7.39)	12.78 (7.26)	26.50 (7.57)	19.64 (5.81)
<b>Observed Case (Population: RS with Observed Cases)</b> Analysis included slotting approach without a specified minimum window between radiograph time points. Placebo mean change value is biased because it includes only subjects who performed well on placebo therapy (ie, did not escape to CZP).				
Mean (SD)	n=58 0.13 (0.39)	n=126 -0.04 (0.64)	n=118 0.07 (0.69)	n=244 0.01 (0.66)
<b>Post-hoc imputation (Population: RS)</b> Imputation included linear extrapolation using median change from Baseline to Week 24 for subjects with less than 2 radiographs and a minimum 8-week window was specified between radiographs.				
LS mean (SE)	0.28 (0.07)	0.01 (0.07)	0.11 (0.08)	0.06 (0.06)

ANCOVA=analysis of covariance; CZP=certolizumab pegol; LS=least square; mTSS=modified total Sharp score; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; SAP=statistical analysis plan; SD=standard deviation; SE=standard error; TNF $\alpha$ =tumor necrosis factor

Note: All analyses used an ANCOVA model with treatment, region, and prior TNF $\alpha$  exposure (yes/no) as factors and Baseline score as covariate.

Data sources: PsA001 Week 24 CSR Table 4.9.1, Table 4.10.1, Post-hoc Table 4.17.2.1, Post-hoc Table 4.9.1.1

Source: Summary of Clinical Efficacy, Table 2-22, page 80.

Dr.Hamilton's statistical review includes a detailed explanation of UCB's proposed post-hoc analyses. In addition, Dr.Hamilton explains why the statistical team rejected UCB's multiple post-hoc analyses.

Instead, the statistical team re-analyzed all the radiographic data using the following strategy. Again, Dr.Hamilton's statistical review will provide much more detail of these post-hoc analyses.

(1) FDA Post-Hoc Analysis #1

For all subjects with mTSS measurements from 2 times points (i.e., 1 missing value), linear extrapolation was used. Subjects with less than 2 mTSS observations were excluded from the analysis completely. Table 17 displays the results from this analysis. With this analysis, CZP 200mg and 400mg appear to have less progression from baseline than the placebo group. The result from the CZP 200mg group is statistically different from placebo, but the result from the CZP 400mg group is not. For the pooled CZP group, the difference from placebo is statistically significant.

**Table 17. Change from Baseline in mTSS at Week 24, Exclusion of Subjects with <2 Available Radiographs (Placebo Escape Data NOT Utilized)**

	PBO <sup>a</sup>	CZP 200mg q2wks	CZP 400mg q4wks	CZP 200mg q2w + CZP 400mg q4w
	N=136	N=138	N=135	N=273
Sample size	n=117	n=130	n=123	n=253
Week 24, mean change from baseline (SE)	0.27 (0.08)	-0.001 (0.08)	0.11 (0.08)	0.05 (0.06)
<b>Week 24, difference from PBO<sup>b</sup></b>				
	-	-0.27	-0.16	-0.21
<b>p-value</b>	-	0.0079	0.1220	0.0156

Randomized Set, NOT Utilizing Placebo Escape Data  
 For PBO, linear extrapolation is used for subjects escaping to CZP.  
 Source: Hamilton K. FDA Primary Statistical Review.

(2) FDA Post-Hoc Analysis #2

Like the first analysis, for all subjects with mTSS measurements from 2 time points, linear extrapolation was used. Subjects with less than 2 mTSS observations were excluded except for those placebo subjects who early escaped. The observed values from the early escape subjects were used. Table 18 presents the results from this analysis. Again, the CZP-treated subjects appeared to have less progression from baseline. Again, the difference from placebo was only statistically significant from the CZP 200mg group. The All CZP group also had statistical significance, although less pronounced than analysis #1.

**Table 18. Change from Baseline in mTSS at Week 24, Exclusion of Subjects with <2 Radiographs (PBO Escape Data Utilized)**

	PBO <sup>a</sup>	CZP 200mg q2wks	CZP 400mg q4wks	CZP 200mg q2w + CZP 400mg q4w
	N=136	N=138	N=135	N=273
Sample size	n=123	n=130	n=123	n=253
Week 24, mean change from baseline (SE)	0.18 (0.07)	-0.02 (0.07)	0.09 (0.07)	0.03 (0.05)
<b>Week 24, difference from PBO<sup>b</sup></b>				
	-	-0.21	-0.10	-0.15
p-value	-	0.0170	0.261	0.0421

Randomized Set, Utilizing Placebo Escape Data  
 For PBO subjects who switched to CZP, their CZP data are utilized for calculation.  
 Source: Hamilton K. FDA Primary Statistical Review.

Post-Hoc Analysis #2 provides a conservative estimate of treatment effect since observed data from the escaped placebo subjects should reflect the step up in therapy, and would serve to reduce the estimated difference between placebo and CZP, if anything. The statistical team feels that this is the preferred analysis in evaluating the radiographic data and has concluded that these data support a conclusion that certolizumab pegol has a favorable effect on structural damage outcomes. This effect appears to be more pronounced with the 200mg q2w dose regimen.

### PASI75

The effect of CZP treatment on psoriatic skin disease was assessed with PASI response. PASI75 response was calculated for all subjects with ≥3% BSA psoriasis at baseline. Table 19 shows the proportion of PASI75 and PASI90 responders at Weeks 12 and 24 for all treatment arms plus the combined CZP treatment group. For both doses of CZP at both time points, there were significantly more PASI75 and PASI90 responders when compared to placebo. Although UCB defined the endpoint to assess the difference of the combined CZP group and placebo, it is more informative to evaluate the doses separately. Like most of the other endpoints discussed thus far, the difference from placebo was smaller for CZP 400mg q4w.

In UCB's prespecified analysis, PASI75 is ranked after change from baseline in mTSS, making assessment of the statistical significance of this endpoint problematic. Additionally, it should be noted that certolizumab pegol (b) (4)

[Redacted]

**Table 19. PASI75 and PASI90 Responders at Weeks 12 and 24 (for subjects with ≥3% BSA of psoriasis at baseline)**

	PBO <sup>a</sup> N=86	CZP 200mg q2wks N=90	CZP 400mg q4wks N=76	CZP 200mg q2w + CZP 400mg q4w N=166
<b>PASI75</b>				
<b>Week 12</b>				
Responders, n (%)	12 (14.0)	42 (46.7)	36 (47.4)	78 (47.0)
Difference from PBO, % (95% CI)	-	32.7 (20.1, 45.4)	33.4 (20.0, 46.8)	33.0 (22.5, 43.6)
p-value	-	<0.001	<0.001	<0.001
<b>Week 24</b>				
Responders, n (%)	13 (15.1)	56 (62.2)	46 (60.5)	102 (61.4)
Difference from PBO, % (95% CI)	-	47.1 (34.6, 59.7)	45.4 (32.1, 58.8)	46.3 (25.7, 56.9)
p-value	-	<0.001	<0.001	<0.001
<b>PASI90</b>				
<b>Week 12</b>				
Responders, n (%)	4 (4.7)	20 (22.2)	15 (19.7)	35 (21.1)
Difference from PBO, % (95% CI)	-	17.6 (7.9, 27.2)	15.1 (5.1, 25.1)	16.4 (8.8, 24.1)
p-value	-	<0.001	0.004	<0.001
<b>Week 24</b>				
Responders, n (%)	5 (5.8)	42 (46.7)	27 (35.5)	69 (41.6)
Difference from PBO, % (95% CI)	-	40.9 (29.4, 52.3)	29.7 (17.9, 41.6)	35.8 (26.8, 44.7)
p-value	-	<0.001	<0.001	<0.001

Randomized Set, with Imputation

a For the entire placebo group, nonresponder imputations (NRI) was used for subjects escaping to CZP

Source: Summary of Clinical Efficacy, Table 2-38, page 110-111.

## 6.1.6 Other Endpoints

### *Dactylitis and Enthesitis*

Dactylitis and enthesitis are important and unique features of PsA that are not captured by the ACR response criteria. Thus, they are considered clinically relevant secondary endpoints even though they are not ranked secondary endpoints.

UCB uses the Leeds Dactylitis Index (LDI) to assess the presence of dactylitis. Table 20 shows the change from baseline in LDI from small subgroup of patients who had dactylitis at baseline. Based on this small subgroup, it is difficult to draw conclusions, although CZP treatment does not appear to have a major effect based on these data.

**Table 20. Change from Baseline in LDI (for subjects with baseline dactylitis) at Weeks 12 and 24**

	<b>PBO<sup>a</sup></b>	<b>CZP 200mg q2wks</b>	<b>CZP 400mg q4wks</b>
	<b>N=45</b>	<b>N=47</b>	<b>N=47</b>
<b>Leeds Dactylitis Index</b>			
<b>Baseline, mean (SD)</b>	2.31 (1.91)	2.14 (1.21)	2.37 (1.87)
<b>Week 12</b>			
<b>Week 12, mean (SD)</b>	2.24 (1.81)	2.32 (3.46)	1.91 (1.00)
<b>Week 12, mean change from baseline (SD)</b>	-0.06 (0.88)	0.18 (3.06)	-0.46 (1.59)
<b>Week 12, difference from PBO<sup>b</sup></b>			
<b>LS mean (SE)</b>	-	0.14 (0.42)	-0.42 (0.42)
<b>95% CI</b>	-	-0.69, 0.98	-1.26, 0.41
<b>p-value</b>	-	0.737	0.319
<b>Week 24</b>			
<b>Week 24, mean (SD)</b>	2.25 (1.82)	2.15 (3.46)	1.91 (0.99)
<b>Week 24, mean change from baseline (SD)</b>	-0.06 (0.97)	0.01 (3.07)	-0.46 (1.59)
<b>Week 24, difference from PBO<sup>b</sup></b>			
<b>LS mean (SE)</b>	-	-0.03 (0.43)	-0.42 (0.43)
<b>95% CI</b>	-	-0.88, 0.81	-1.26, 0.43
<b>p-value</b>	-	0.938	0.328

Randomized Set, with Imputation

a For the entire PBO group, last observation prior to escape was carried forward for subjects escaping to CZP

b ANCOVA model with treatment, region, and prior anti-TNF $\alpha$  exposure (yes/no) as factors and baseline score as covariate

Source: Summary of Clinical Efficacy, Table 2-17, page 71; PSA001 Week 24 CSR Table 4.32, pages 717, 721

A larger subgroup of PsA patients had enthesitis at baseline, and the Leeds Enthesitis Index (LEI) was used to evaluate the effect of treatment on this manifestation. Table 21 displays the LEI scores for all treatment arms and the change from baseline at Weeks 12 and 24. In contrast to the dactylitis results, although all the treatment arms (including placebo) seemed to have an improvement from baseline, CZP-treatment was associated with a greater improvement compared to placebo. The difference from placebo for both CZP dose groups is statistically significant.

**Table 21. Change from Baseline in LEI (for subjects with baseline enthesitis) at Weeks 12 and 24**

	<b>PBO<sup>a</sup></b>	<b>CZP 200mg q2wks</b>	<b>CZP 400mg q4wks</b>
	<b>N=91</b>	<b>N=88</b>	<b>N=84</b>
<b>Leeds Enthesitis Index</b>			
<b>Baseline, mean (SD)</b>	2.96 (1.6)	3.1 (1.7)	2.9 (1.6)
<b>Week 12</b>			
<b>Week 12, mean (SD)</b>	2.1 (1.9)	1.2 (1.8)	1.3 (1.7)
<b>Week 12, mean change from baseline (SD)</b>	-0.9 (2.0)	-1.8 (1.8)	-1.7 (1.8)
<b>Week 12, difference from PBO<sup>b</sup></b>			
<b>LS mean (SE)</b>	-	-0.9 (0.2)	-0.8 (0.2)
<b>95% CI</b>	-	-1.4, -0.4	-1.3, 0.3
<b>p-value</b>	-	<0.001	0.002
<b>Week 24</b>			
<b>Week 24, mean (SD)</b>	1.8 (1.8)	1.0 (1.7)	1.1 (1.8)
<b>Week 24, mean change from baseline (SD)</b>	-1.1 (1.8)	-2.0 (1.8)	-1.8 (1.9)
<b>Week 24, difference from PBO<sup>b</sup></b>			
<b>LS mean (SE)</b>	-	-0.9 (0.2)	-0.7 (0.2)
<b>95% CI</b>	-	-1.3, -0.4	-1.2, -0.3
<b>p-value</b>	-	<0.001	0.003

Randomized Set, with Imputation

a For the entire PBO group, last observation prior to escape was carried forward for subjects escaping to CZP

b ANCOVA model with treatment, region, and prior anti-TNF $\alpha$  exposure (yes/no) as factors and baseline score as covariate

Source: Summary of Clinical Efficacy, Table 2-18, page 73; PSA001 Week 24 CSR Table 4.33, page 727, 730.

### SF-36

SF-36 is a general measure of health status that has been used in rheumatoid arthritis studies since the 1990s. An explanation of scoring is described in Appendix 9.5. SF-36 was not pre-specified as a ranked secondary endpoint in the statistical hierarchy

Table 22 displays the results of the SF-36, the SF-36 physical component, and the SF-35 mental component along with the change from baseline and then the difference of the CZP results from placebo. A higher score indicates better health. Essentially, for all of the variables, there is a higher score in all treatment arms (including placebo). There is a significant difference from placebo for both doses of CZP.

Table 22. SF-36 at Weeks 12 and 24

	PBO <sup>a</sup> N=136	CZP 200mg q2wks N=138	CZP 400mg q4wks N=135
<b>SF-36</b>			
Baseline, mean (SD)	33.74 (10.27)	34.11 (9.89)	33.45 (9.90)
<b>Week 12</b>			
Week 12, mean (SD)	34.88 (10.69)	40.90 (11.29)	39.56 (11.26)
Week 12, mean change from baseline (SD)	1.14 (7.73)	6.79 (9.86)	6.10 (9.00)
Week 12, difference from PBO <sup>b</sup>			
LS mean (SE)	-	5.64 (0.87)	4.82 (0.88)
95% CI	-	3.92, 7.35	3.09, 6.54
p-value	-	<0.001	<0.001
<b>Week 24</b>			
Week 24, mean (SD)	35.23 (10.93)	41.17 (11.94)	41.00 (10.66)
Week 24, mean change from baseline (SD)	1.50 (8.34)	7.05 (11.21)	7.54 (9.22)
Week 24, difference from PBO <sup>b</sup>			
LS mean (SE)	-	6.13 (0.96)	5.29 (0.97)
95% CI	-	4.24, 8.02	3.39, 7.19
p-value	-	<0.001	<0.001
<b>SF-36 PCS</b>			
Baseline, mean (SD)	33.79 (7.93)	33.07 (7.73)	33.24 (7.50)
<b>Week 12</b>			
Week 12, mean (SD)	35.56 (8.10)	40.59 (9.36)	39.93 (9.64)
Week 12, mean change from baseline (SD)	1.77 (6.11)	7.53 (9.09)	6.69 (7.66)
Week 12, difference from PBO <sup>b</sup>			
LS mean (SE)	-	5.83 (1.02)	4.94 (1.03)
95% CI	-	3.82, 7.84	2.92, 6.96
p-value	-	<0.001	<0.001
<b>Week 24</b>			
Week 24, mean (SD)	35.93 (8.59)	41.50 (9.98)	40.82 (9.66)
Week 24, mean change from baseline (SD)	2.14 (7.18)	8.43 (10.10)	7.58 (8.06)
Week 24, difference from PBO <sup>b</sup>			
LS mean (SE)	-	5.76 (1.09)	5.99 (1.09)
95% CI	-	3.62, 7.90	3.84, 8.14
p-value	-	<0.001	<0.001
<b>SF-36 MCS</b>			
Baseline, mean (SD)	42.36 (12.45)	40.74 (11.17)	41.87 (12.52)
<b>Week 12</b>			
Week 12, mean (SD)	43.72 (11.85)	45.61 (12.21)	44.27 (12.77)
Week 12, mean change from baseline (SD)	1.36 (8.63)	4.87 (10.00)	2.40 (8.70)
Week 12, difference from PBO <sup>b</sup>			
LS mean (SE)	-	3.10 (1.04)	0.84 (1.04)
95% CI	-	1.06, 5.13	-1.20, 2.89
p-value	-	0.003	0.417
<b>Week 24</b>			
Week 24, mean (SD)	43.10 (12.02)	46.24 (12.22)	45.36 (13.14)
Week 24, mean change from baseline (SD)	0.73 (9.85)	5.49 (10.21)	3.49 (9.62)
Week 24, difference from PBO <sup>b</sup>			
LS mean (SE)	-	4.32 (1.11)	2.50 (1.11)

<b>95% CI</b>	-	2.13, 6.50	0.31, 4.70
<b>p-value</b>	-	<0.001	0.025

Randomized Set, with Imputation

a For the entire PBO group, last observation prior to escape was carried forward for subjects escaping to CZP

b ANCOVA model with treatment, region, and prior anti-TNF $\alpha$  exposure (yes/no) as factors and baseline score as covariate

Source: Summary of Clinical Efficacy, Table 2-28, page 91; Table 2-29, page 93; Table 2-31, page 97.

PSA001 Week 24 CSR Table 4.35.1., pages 746, 749; Table 4.36.1, pages 753, 756; Table 4.37.1, pages 760, 763.

The MCID identified for the SF-36 MCS and PCS is  $\geq 2.5$  points (Strand et al., 2005). Thus, in Table 24 below, any subject with an improvement in SF-36 measurement that is  $\geq 2.5$  points was counted as a “responder.” At Week 12, there were significantly more SF-36 physical component responders in the CZP groups than placebo. However, the difference is not significant for the mental component. On the other hand, at Week 24, the proportion of SF-36 PCS and MCS responders was significantly higher in the CZP treatment arms than in placebo.

**Table 23. SF-36 PCS and MCS Responders at Weeks 12 and 24**

MCID $\geq 2.5$ points <sup>1</sup>	PBO <sup>a</sup> N=136	CZP 200mg q2wks N=138	CZP 400mg q4wks N=138
<b>SF-36 PCS responders</b>			
<b>Week 12</b>			
Responders, n (%)	57 (41.9)	91 (65.9)	91 (67.4)
Difference from PBO, % (95% CI)	-	24.0 (12.6, 35.5)	25.5 (14.0, 37.0)
p-value	-	<0.001	<0.001
<b>Week 24</b>			
Responders, n (%)	41 (30.1)	88 (63.8)	97 (71.9)
Difference from PBO, % (95% CI)	-	33.6 (22.5, 44.7)	41.7 (30.9, 52.5)
p-value	-	<0.001	<0.001
<b>SF-36 MCS responders</b>			
<b>Week 12</b>			
Responders, n (%)	50 (36.8)	67 (48.6)	64 (47.4)
Difference from PBO, % (95% CI)	-	11.8 (0.2, 23.4)	10.6 (-0.1, 22.3)
p-value	-	0.048	0.076
<b>Week 24</b>			
Responders, n (%)	31 (22.8)	75 (54.3)	66 (48.9)
Difference from PBO, % (95% CI)	-	31.6 (20.7, 42.5)	26.1 (15.1, 37.1)
p-value	-	<0.001	<0.001

Randomized Set, with Imputation

<sup>1</sup> Strand et al., 2005.

a For the entire placebo group, nonresponder imputations (NRI) was used for subjects escaping to CZP

Source: Summary of Clinical Efficacy, Table 2-30, page 95; Table 2-32, page 98.

Although CZP-treatment appears to be associated with an improvement in these SF-36 results, discussions are ongoing about the best and clinically interpretable ways to reflect SF-36 results, which are based on 8 individual domains, (b) (4)

(b) (4)

*Fatigue Assessment Scale (FAS)*

In PsA001, UCB used the Fatigue Assessment Scale (FAS) as a measurement of fatigue. A higher score is reflective of greater fatigue. (b) (4) the FAS endpoints were not in the pre-specified ranked secondary endpoints.

Table 24 displays the change from baseline in FAS at Weeks 12 and 24. All treatment arms show an improvement in the FAS measurement at both time points. However, the CZP treatment arms had significantly greater improvement than the placebo arm.

**Table 24. Change from Baseline in FAS at Weeks 12 and 24**

	PBO <sup>a</sup> N=136	CZP 200mg q2wks N=138	CZP 400mg q4wks N=135
<b>FAS</b>			
<b>Baseline, mean (SD)</b>	5.8 (2.0)	6.3 (2.0)	6.2 (2.1)
<b>Week 12</b>			
<b>Week 12, mean (SD)</b>	5.5 (2.3)	4.3 (2.3)	4.8 (2.4)
<b>Week 12, mean change from baseline (SD)</b>	-0.3 (2.2)	-2.1 (2.3)	-1.4 (2.1)
<b>Week 12, difference from PBO<sup>b</sup></b>			
<b>LS mean (SE)</b>	-	-1.5 (0.2)	-0.9 (0.2)
<b>95% CI</b>	-	-2.0, -1.0	-1.4, -0.4
<b>p-value</b>	-	<0.001	<0.001
<b>Week 24</b>			
<b>Week 24, mean (SD)</b>	5.2 (2.4)	4.1 (2.5)	4.3 (2.5)
<b>Week 24, mean change from baseline (SD)</b>	-0.6 (2.3)	-2.2 (2.6)	-1.9 (2.3)
<b>Week 24, difference from PBO<sup>b</sup></b>			
<b>LS mean (SE)</b>	-	-1.3 (0.3)	-1.1 (0.3)
<b>95% CI</b>	-	-1.9, -0.8	-1.6, -0.5
<b>p-value</b>	-	<0.001	<0.001

Randomized Set, with Imputation

a For the entire PBO group, last observation prior to escape was carried forward for subjects escaping to CZP

b ANCOVA model with treatment, region, and prior anti-TNF $\alpha$  exposure (yes/no) as factors and baseline score as covariate

Source: Summary of Clinical Efficacy, Table 2-34, page 101; PSA001 Week 24 CSR Table 4.34, page 738, 742.

The MCID in the fatigue assessment scale is a change of 1 point (Belza 1990). Table 25 summarizes the proportion of FAS responders as defined by this MCID. CZP-treatment was associated with a higher proportion of responders compared to placebo, and the difference was statistically significant at both time points.

**Table 25. FAS Responders at Weeks 12 and 24**

MCID $\geq$ 1 point <sup>1</sup>	PBO <sup>a</sup> N=136	CZP 200mg q2wks N=138	CZP 400mg q4wks N=138
<b>Week 12</b>			
Responders, n (%)	53 (39.0)	95 (68.8)	75 (55.6)
Difference from PBO, % (95% CI)	-	29.9 (18.6, 41.1)	16.6 (4.9, 28.3)
p-value	-	<0.001	0.006
<b>Week 24</b>			
Responders, n (%)	39 (28.7)	91 (65.9)	85 (63.0)
Difference from PBO, % (95% CI)	-	37.3 (26.3, 48.2)	34.4 (23.1, 45.4)
p-value	-	<0.001	<0.001

Randomized Set, with Imputation

<sup>1</sup> Belza 1990.

<sup>a</sup> For the entire placebo group, nonresponder imputations (NRI) was used for subjects escaping to CZP

Source: Summary of Clinical Efficacy, Table 2-35, page 103.

Many additional secondary endpoints were included (b) (4) and were not included in the endpoint hierarchy. These will not be discussed in detail in this review.

### 6.1.7 Subpopulations

For ACR 20 response and change from baseline in mTSS, various subgroup analyses were performed. In the section below, only subgroup analyses of the primary endpoint (ACR 20 response) will be discussed. Subgroup analyses for the mTSS are difficult to interpret because they were provided based on the applicant's post-hoc analyses that were not considered appropriate by the statistical review team.

#### *Prior and Concomitant DMARDs*

Table 26 presents ACR 20 responders at Week 12 by concomitant and previous DMARD use (as a whole). Irrespective of concomitant or prior DMARD use, a higher proportion of CZP-treated patients experienced an ACR20 response compared to placebo-treated patients. The difference was statistically significant in each subgroup.

**Table 26. ACR 20 Responders at Week 12 by Concomitant and Prior DMARDs**

	<b>PBO<sup>a</sup></b>	<b>CZP 200mg q2wks</b>	<b>CZP 400mg q4wks</b>
% of responders	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>
<b>Concomitant use of allowed DMARDs at Baseline</b>			
<b>No, n (%)</b>	8/52 (15.4)	26/44 (59.1)	17/44 (38.6)
<b>Difference to PBO, %</b>	-	43.7	23.3
<b>(95% CI)<sup>a</sup></b>		(26.2, 61.2)	(5.8, 40.7)
<b>p-value<sup>a</sup></b>	-	<0.001	0.011
<b>Yes, n (%)</b>	25.84 (29.8)	54/94 (57.4)	53/91 (58.2)
<b>Difference to PBO, %</b>	-	27.7	28.5
<b>(95% CI)<sup>a</sup></b>		(13.7, 41.7)	(14.4, 42.6)
<b>p-value<sup>a</sup></b>	-	<0.001	<0.001
<b>Prior Use of DMARDs</b>			
<b>1, n (%)</b>	22/74 (29.7)	42/61 (68.9)	42/72 (58.3)
<b>Difference to PBO, %</b>	-	39.1	28.6
<b>(95% CI)<sup>a</sup></b>		(23.5, 54.7)	(13.2, 44.0)
<b>p-value<sup>a</sup></b>	-	<0.001	<0.001
<b>≥2, n (%)</b>	11/60 (18.3)	38/73 (52.1)	28/60 (46.7)
<b>Difference to PBO, %</b>	-	33.7	28.3
<b>(95% CI)<sup>a</sup></b>		(18.6, 48.8)	(12.4, 44.3)
<b>p-value<sup>a</sup></b>	-	<0.001	<0.001

Randomized Set, with Imputation

a Treatment difference: CZP 200mg q2w-PBO, CZP 400mg q4w-PBO (and corresponding 95% CI and p-value) were estimated using a standard 2-sided Wald asymptomatic test with a 5% alpha level. The corresponding 95% CI for the differences were constructed using their asymptomatic standard errors (asymptomatic Wald confidence limits).

Source: Summary of Clinical Efficacy, Table 2-43, page 125.

### *Prior Anti-TNF $\alpha$ Therapy*

The proportion of ACR20 responders by previous anti-TNF $\alpha$  therapy is presented in Table 27. Irrespective of prior TNF inhibitor use, at both Week 12 and Week 24, a higher proportion of CZP-treated patients experienced an ACR20 compared to placebo. The difference was statistically significant in each subgroup.

**Table 27. ACR 20 Responders at Week 12 and 24 Based on Prior Anti-TNF $\alpha$  Therapy**

	<b>PBO<sup>a</sup></b>	<b>CZP 200mg q2wks</b>	<b>CZP 400mg q4wks</b>
% of responders by prior anti-TNF $\alpha$ therapy	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>
<b>Week 12</b>			
<b>No, n (%)</b>	29/110 (26.4)	66/107 (61.7)	55/112 (49.1)
<b>Difference to PBO, %</b>	-	35.3	22.7
<b>(95% CI)<sup>a</sup></b>	-	(23.0, 47.7)	(10.4, 35.1)
<b>p-value<sup>a</sup></b>	-	<0.001	<0.001
<b>Yes, n (%)</b>	4/26 (15.4)	14/31 (45.2)	15/23 (65.2)
<b>Difference to PBO, %</b>	-	29.8	49.8
<b>(95% CI)<sup>a</sup></b>	-	(7.4, 52.1)	(25.9, 73.7)
<b>p-value<sup>a</sup></b>	-	0.012	<0.001
<b>Week 24</b>			
<b>No, n (%)</b>	29/110 (26.4)	69/107 (64.5)	63/112 (56.3)
<b>Difference to PBO, %</b>	-	38.1	29.9
<b>(95% CI)<sup>a</sup></b>	-	(25.9, 50.4)	(17.5, 42.2)
<b>p-value<sup>a</sup></b>	-	<0.001	<0.001
<b>Yes, n (%)</b>	3/26 (11.5)	19/31 (61.3)	13/23 (56.5)
<b>Difference to PBO, %</b>	-	49.8	45.0
<b>(95% CI)<sup>a</sup></b>	-	(28.7, 70.8)	(21.3, 68.7)
<b>p-value<sup>a</sup></b>	-	<0.001	<0.001

Randomized Set, with Imputation

<sup>a</sup> Treatment difference: CZP 200mg q2w-PBO, CZP 400mg q4w-PBO (and corresponding 95% CI and p-value) were estimated using a standard 2-sided Wald asymptomatic test with a 5% alpha level. The corresponding 95% CI for the differences were constructed using their asymptomatic standard errors (asymptomatic Wald confidence limits).

Source: Summary of Clinical Efficacy, Table 2-44, page 127.

### *Immunogenicity*

Approximately 10.8% of subjects exposed to CZP developed a positive anti-CZP antibody status. Table 28 displays the effects of the presence of anti-CZP antibody on ACR 20 response. Although the number of patients with anti-CZP antibodies is small, anti-CZP antibody status did not appear to negatively impact the proportion of ACR20 responders in the CZP treatment groups.

**Table 28. ACR 20 Responders by Anti-CZP Antibody Status**

	<b>PBO<sup>a</sup></b>	<b>CZP 200mg q2wks</b>	<b>CZP 400mg q4wks</b>
% of responders	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>
<b>Anti-CZP antibody status<sup>b</sup></b>			
<b>Negative, n (%)</b>	32/129 (24.8)	71/122 (58.2)	61/119 (51.3)
<b>Difference to PBO, %</b>	-	33.4	26.5
<b>(95% CI)<sup>a</sup></b>	-	(21.9, 44.9)	(14.8, 38.1)
<b>p-value<sup>a</sup></b>	-	<0.001	<0.001
<b>Positive, n (%)</b>	1/7 (14.3)	9/16 (56.3)	9/16 (56.4)
<b>Difference to PBO, %</b>	-	42.0	42.0
<b>(95% CI)<sup>a</sup></b>	-	(6.4, 77.5)	(6.4, 77.5)
<b>p-value<sup>a</sup></b>	-	0.048	0.048

Randomized Set, with Imputation

a Treatment difference: CZP 200mg q2w-PBO, CZP 400mg q4w-PBO (and corresponding 95% CI and p-value) were estimated using a standard 2-sided Wald asymptomatic test with a 5% alpha level. The corresponding 95% CI for the differences were constructed using their asymptomatic standard errors (asymptomatic Wald confidence limits).

b Subjects who were positive for anti-CZP antibodies at any time during the study were counted in the positive subgroup. In the PBO group, subjects who escaped to CZP and became anti-CZP positive were counted in the PBO group as positive.

Source: Summary of Clinical Efficacy, Table 2-43, page 125-126.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

UCB proposes that the dose should be 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and week 2 and 4, followed by 200mg every other week (b) (4)

The Division does not agree with this proposed dose. In the above Sections 6.1.4 through 6.1.6, multiple efficacy variables are discussed. For all of the primary and key secondary variables (listed below), the CZP 400mg q4w treatment arm had a numerically lower treatment effect than the CZP 200mg q2w arm. Similarly, for radiographic inhibition, the CZP 400mg q4w treatment arm was associated with a numerically lower treatment effect, which was not statistically significant.

- ACR 20 Response at Week 12 and 24
- Change from baseline of HAQ-DI at Week 24
- Change from baseline of mTSS at Week 24
- PASI75 Response at Week 24

Therefore, the dosing recommendations should be consistent with the RA dosing recommendations, which are as follows:

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.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No data beyond Week 24 are presented in this submission. ACR 20, ACR 50, and ACR 70 responses are discussed in Section 6.1.4.

Anti-CZP antibody positivity is associated with decreased plasma concentration and, thus, could be associated with reduced efficacy. The evaluation of anti-CZP antibody status on treatment effect in PsA001 is discussed above in Section 6.1.7. In the RA studies, the presence of anti-CZP antibody was associated with a reduced ACR 20 response but no difference in radiographic response from the primary analysis.

### 6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues or analyses will be reviewed.

## 7 Review of Safety

### Safety Summary

In the PsA trials, 273 subjects were randomized to certolizumab pegol; after early escape and the week 24 cross-over, 332 subjects were exposed to study drug through the 24-week Double-Blind Treatment Period. The mean number of doses of certolizumab received was 11.2 in the CZP 200mg group and 6.5 in the CZP 400mg group. If exposure is defined by the maintenance interval, the estimated duration of exposure of certolizumab pegol is 28-56 days. Through the clinical cutoff date of 31 May 2013, 358 subjects received >6 months of CZP, and 279 subjects received >12 months of CZP.

Although the amount of safety data is limited, it is adequate to describe the safety profile of certolizumab in PsA, and to determine whether this safety profile is similar to the known safety profile of certolizumab.

### Major Safety Results:

The review of the clinical safety data indicates that the findings in PsA are consistent with the findings in the known safety profile of certolizumab pegol in the approved indications of RA and Crohn's Disease. In addition, the findings are consistent with the general safety profile of anti-TNF $\alpha$  therapy.

Deaths: There were 2 deaths in the PsA trials in the double-blind treatment period (both in the CZP treatment groups) and a total of 6 deaths through the data cutoff date. The

types of deaths (infections, malignancies, cardiac disorders) are consistent with those seen in other trials of biologic immunosuppressives in PsA.

Serious Adverse Events (SAEs): The numbers of nonfatal serious adverse events (SAEs) and AEs leading to discontinuation were higher in the CZP-treated subjects. For both categories of adverse events, the most common SOC was Infections and Infestations. Given that risk of infections is a well-known toxicity of TNF $\alpha$  inhibitors, this is not a new safety signal.

Serious Infections: Through the end of the reporting period, the exposure-adjusted incidence of serious infections was 1.74 and 3.14 per 100 patient-years for CZP 200mg and CZP 400mg respectively. The rate of serious infections in RA patients on ant-TNF $\alpha$  has been estimated at 5-6 per 100 patient-years (Dixon 2007). Thus, the findings in PsA001 are consistent with what is seen in other TNF inhibitors.

Through the data cutoff date, there were 3 opportunistic infections – 2 cases of HIV and 1 case of ophthalmic herpes (nonserious). In addition, there were 8 cases of PPD conversions of which 5 might be consistent with latent TB. There were no cases of active TB through the data cutoff date.

Malignancies: In the Double-Blind Treatment period, there were 2 malignancies (cervical carcinoma stage 0 and breast CA). Through the data cutoff date, there was an additional 4 malignancies (2 cases of breast CA, thyroid CA, lymphoma). Through the data cutoff date, the exposure-adjusted incidence was 0.87 and 1.33 per 100 patient-years for CZP 200mg and 400mg respectively. Overall, these findings are consistent with the experience of other TNF inhibitors in other rheumatic disease.

Cardiovascular events: Through the end of the reporting period, the exposure-adjusted incidence rate of CV events was 2.62 per 100 patient-years for CZP 200mg and 1.80 per 100 subject-years for CZP 400mg. There were no cases of isolated heart failure (i.e., not in the setting of concomitant myocardial infarction). Patients with PsA are at increased risk of CV disease, so these findings do not seem greater than what is expected.

Immunogenicity: Overall, immunogenicity is consistent with what has been seen in other biologic therapy. Through Week 24, 10.8% of subjects exposed to CZP had a positive anti-drug antibody status.

Allergic Reactions: The number of injection site reactions is low. Through the controlled portion, there were more local injection site reactions in subjects who received CZP. However, the number of systemic reactions was similar across treatment arms.

Other Events of Interest (Demyelinating Disorders, Autoimmune Disorders, Serious Hematologic Cytopenias, Hepatotoxicity): There was 1 case of cutaneous lupus

erythematosus. Otherwise, there were no cases of serious skin disorders or autoimmune disease. There were no cases of demyelinating disease or other significant neurologic diagnoses. Lastly, there were no cases of Hy's law. The number of subjects with elevated liver enzymes (particularly, the higher elevations) was actually relatively similar across treatment arms. Similarly, lymphopenia was the most common hematologic abnormality but was actually more frequently seen in the placebo arm.

**Summary:** Overall, the types and rates of adverse events submitted with this supplement are consistent with those reviewed with the original BLA. No new safety signals have been identified. Exposure-adjusted incidence rates of death, SAEs, serious infections, malignancies are similar to the original BLA. Laboratory abnormalities and outcomes are consistent with the original BLA. Essentially, the types of AEs are consistent with the original BLA and the underlying patient population.

## 7.1 Methods

Sections 7.1.1, 7.1.2, and 7.1.3 below detail the methods supporting this safety review. The clinical safety data utilized in the analysis and the categorization of adverse events are described.

The safety assessments for the completed double-blind treatment period (through Week 24) included AEs, laboratory parameters (serum chemistry, hematology, and urinalysis), vital signs (blood pressure, pulse, respiratory rate, and temperature), physical examination (as recorded on the case report form at Screening), and TB testing. As noted below, AEs and markedly abnormal laboratory data were assessed for all completed safety visits in the other safety periods through cutoff date of 31 May 2012.

Exposure differed between the Double-Blind treatment period and the data cutoff date (Double Blind Safety Pool and All CZP Safety Pool, defined below). In the analysis and review, some adverse events were adjusted for exposure and reported by 100 patient-years exposure. Two approaches were conducted in attempts to adjust for exposure. The first approach used only the first occurrence of an AE with corresponding exposure, and this was called the *exposure-adjusted incidence*. In other words, for the exposure-adjusted incidence rates, the first occurrence of an AE for a certain group was divided by the sum of exposure for all subjects to the respective dose group. The exposure for subjects who experienced the respective AE was censored to time of occurrence of that particular AE. The unit for exposure-adjusted incidence rates was number of subjects. The second approach used all AEs and the entire exposure; this was called *exposure-adjusted event rate*. For exposure-adjusted event rates, all AEs for a treatment group were utilized, even if that meant that one subject had the same AE on 3 separate occasions. All 3 AEs would be counted. All AEs were then divided by the sum of exposure of all subjects to the respective dose group. The statistical unit was exposure to study treatment.

All statistical analyses were performed using SAS (STATISTICAL ANALYSIS SYSTEM). Analyses used descriptive methods, such as frequency distributions of dichotomous and categorical variables (ordered or nominal) containing the number of observations and the corresponding percentages. In addition, analyses often entailed the distribution parameters of continuous variables to include the number of observations, mean, standard deviation, median, and minimum/maximum values. In general, the denominator for percentages was the number of subjects in relevant clinical cut pool. Also, the baseline values were the last valid measurement before study medication administration for the completed Double-Blind period and the clinical cut pools. Some variables were only assessed at screening, so the baseline value utilized this screening value. These instances were specified. Rules for imputation of missing or incomplete data were detailed in the “Statistics” section of Discussion of Individual Studies/Clinical Trials (Section 5.1.3). Typically, the worst case approach was applied for missing values of seriousness, intensity, and relationship.

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

UCB’s PsA clinical program consists of a single clinical study PsA001. Therefore, all safety data reviewed for this current submission was derived from study PsA001 (detailed in Section 5.3). As PsA001 is an ongoing study, the available data in this package include safety data beyond the Double-Blind Treatment Period through data cutoff date of 31 May 2012. No subjects completed the Open Label Period by this cutoff date, but there were subjects who completed the other areas.

#### 7.1.2 Categorization of Adverse Events

Adverse events and markedly abnormal laboratory data were assessed through a data cutoff date of 31 May 2012. This submission contains clinical safety data on Adverse Events (AEs), Serious Adverse Events (SAEs), and adverse events of interest. UCB, Inc. has used the Medical Dictionary for Regulatory Activities (MedDRA), version 14.1, for coding of AEs and conditions in the medical history. The World Health Organization (WHO) Drug Dictionary version March 2010 was used for medications. The Rheumatology Common Toxicity Criteria (RCTC) was utilized for identification of markedly abnormal laboratory values.

An adverse event was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. All adverse events that occurred during the study including screening and follow-up periods (usually, 70 days after the last dose of investigational product), were reported in case report forms (CRFs) even if no study medication was administered. Of note, signs and symptoms of active PsA were only recorded as an AE if it was different in nature (frequency or intensity) from the subject’s baseline.

A serious adverse event (SAE) was defined as meeting one of the following criteria:

- 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 or subject 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 emergency room visit would qualify only if it resulted in a hospital admission.

Adverse events of interest are those that are listed in the European Risk Management Plan.

After assessing adverse events, safety data were presented in different ways based on randomization and treatment.

- “Clinical cut” pools are defined by subjects as they were randomized at Week 0, Week 16, or Week 24.
  - SS is used to describe all randomized subjects who received at least 1 dose of study medication (CZP or placebo). These are the subject groups as defined in the Statistical Analysis Plan.
- Double-Blind Safety Pool included subjects who received at least 1 dose of CZP in the completed Double-Blind Treatment Period (i.e., through Week 24). Thus, placebo subjects who escaped were included in the treatment group (CZP 200mg or CZP 400mg).
- All CZP Safety Pool included subjects who received at least 1 dose of CZP through data cutoff date, 31 May 2012. Thus, data from all periods of the study (Double-Blind, Dose-Blind, and Open-Label) were utilized.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety data from this single Phase 3 study is supported by safety data from the large RA program and 2 completed psoriasis studies. The RA data were pooled from 14 RA studies (12 completed and 2 ongoing with a data cutoff date of 30 November 2011) that include 4049 subjects and 9277 patient-years. In addition, there are 2 completed psoriasis studies (C87040 and C87044) that include 117 subjects with at least 1 exposure, 105 subjects exposed for a total of 12 weeks of double-blind treatment, and 62 subjects exposed for an additional 12 weeks of open-label treatment.

(b) (4)

## 7.2 Adequacy of Safety Assessments

In the ongoing study, PsA001, a total of 393 subjects have been exposed to at least 1 dose of CZP. In addition, there are the supportive safety data (4049 subjects in 14 pooled RA studies) described above in Section 7.1.3. Overall, the safety coding and safety datasets and tabulations are adequate to enable review.

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The extent of exposure for study PsA001 is summarized through the Double-Blind Treatment Period in Table 29. Exposure was defined by period during which medication was administered plus the maintenance interval (14 or 28 days, “narrow sense”) or plus 5 half-lives (70 days, “broader sense”). In terms of weeks, the narrow or broad definition of exposure did not make too much difference. In the Double-Blind Treatment Period (as randomized), the CZP groups were exposed for a little over 20 weeks for a total of 132.7 patient-years. In comparing CZP exposure in the Double-Blind Safety Pool Exposure (as treated, Double-Blind period) and in the All CZP Safety Pool (data cutoff date, as treated), the patient-years of exposure while on CZP treatment was 131.6 year and 458.7 years respectively. Exposure was extended by 39.3 weeks (in the “narrow sense”) and 40.5 weeks (in the “broader sense”).

**Table 29. Exposure in the Double-blind Treatment Period for PsA001**

Exposure in the Double-Blind Treatment Period (Weeks 0-24)				
	PBO <sup>a</sup>	CZP 200mg q2w	CZP 400mg q2w	All CZP <sup>b</sup>
	N=136	N=138	N=135	N=332
<b>Patient-years of exposure</b>	51.1	67.4	65.3	132.7
<b>Number of doses received</b>				
Mean (SD)	9.2 (2.7)	11.2 (1.9)	6.5 (1.2)	7.9 (3.3)
<b>Duration of exposure in narrow sense (weeks)<sup>c</sup></b>				
Mean (SD)	18 (5.4)	23.0 (3.5)	22.6 (4.4)	20.1 (6.7)
<b>Duration of exposure in broad sense (weeks)<sup>d</sup></b>				
Mean (SD)	19.7 (4.3)	23.6 (1.9)	23.4 (2.9)	20.8 (6.4)

a For the entire PBO group, PBO exposure will end with date of 1<sup>st</sup> CZP injection for subjects escaping

b CZP 200mg q2w, CZP 400mg q4w, escaped PBO subjects with their CZP data

c Exposure in the narrow sense = last injection-first injection date + 14 (or 28) days [maintenance interval]

d Exposure in the broader sense = last injection date-first injection date + 70 days (5 half-lives)

Source: Summary of Clinical Safety, Table 1 4, page 30.

Table 30 presents the duration of exposure to CZP through the data cutoff date. A total of 358 subjects were exposed to over 6 months of CZP, and 279 subjects had over 12

months of exposure. Only 1.3% of subjects treated with CZP had over 2 years of exposure.

**Table 30. Duration of Exposure in All CZP groups**

Duration of exposure in All CZP Pool (through data cut-off: 31 May 2012)			
	CZP 200mg q2w	CZP 400mg q2w	All CZP
	N=197	N=196	N=393
Total study drug duration of exposure	n (%) [patient years]	n (%) [patient years]	n (%) [patient years]
>0 months	197 (100.0) [224]	196 (100.0) [219]	393 (100.0) [443]
>6 months	182 (92.4) [220]	176 (89.8) [214]	358 (91.1) [434]
>12 months	139 (70.6) [186]	140 (71.4) [187]	279 (71.0) [373]
>24 months	1 (0.5) [2]	4 (2.0) [8]	5 (1.3) [10]
Duration of exposure	n (%) [patient years]	n (%) [patient years]	n (%) [patient years]
<3 months	8 (4.1)	12 (6.1)	20 (5.1)
≥3 to <6 months	7 (3.6)	8 (4.1)	15 (3.8)
≥6 to <12 months	43 (21.8)	36 (18.4)	79 (20.1)
≥12 to <18 months	95 (48.2)	109 (55.6)	204 (51.9)
≥18 to <24 months	43 (21.8)	27 (13.8)	70 (17.8)
≥24 months	1 (0.5)	4 (2.0)	5 (1.3)

Total study drug duration=sum of each subject's study drug duration within a treatment group  
 Subject's study drug duration = (date of last dose-date of first dose) + 1 maintenance dosing interval  
 Source: PSA001 Summary of Clinical Safety, Table 1-6, page 33.

In summary, the overall exposure data in this submission is adequate for assessment of safety.

### 7.2.2 Explorations for Dose Response

This submission includes limited data on dose response, as only 2 doses (200mg q2w and 400mg q4w, essentially the same cumulative dose) of ustekinumab were studied in PsA001. These were the same doses studied in the RA program. In general, the safety findings appear to be similar in both doses.

### 7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was submitted or expected for this sBLA.

### 7.2.4 Routine Clinical Testing

Clinical testing is detailed in Appendix 9.4 (Schedule of Assessments). Most clinic visits will entail routine laboratory tests (hematology, chemistry, urinalysis), vital signs (blood pressure, respiratory rate, pulse), and physical examination. Pregnancy testing and TB testing were performed regularly. Subjects were monitored for adverse events at every visit.

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the original BLA for review of the original pharmacokinetic properties of this product.

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

**Multiple TNF $\alpha$  inhibitors have been approved to treat a variety of autoimmune disorders such as RA, ankylosing spondylitis, Crohn's Disease, and psoriasis. Treatment with ant-TNF $\alpha$  monoclonal antibody biologics, such as infliximab (Remicade), adalimumab (Humira), and golimumab (Simponi), or with the fusion protein etanercept (Enbrel), has a well-characterized safety profile. In addition, certolizumab pegol (Cimzia) itself has been approved and on the market since 2008 (see Section**

8 Postmarket Experience). First, as an immunosuppressive, infection is a concern. Serious infections, including patients with latent Mycobacterium tuberculosis (TB) infection who are vulnerable to reactivation, are a known risk of TNF $\alpha$ -inhibitor therapy. The current labeling for TNF $\alpha$  inhibitors includes a BOXED WARNING that highlights the risk for serious infections including TB, invasive fungal infections, and other opportunistic infections with the concern that some have been fatal. Also, in the Warnings and Precautions section, there is a warning about Hepatitis B reactivation.

In addition to infection, the immune system has a key role in surveillance for malignancy. The role of TNF $\alpha$  inhibitors in triggering apoptosis of some tumor cell types have been reported in this class of biologic therapy. Patients with RA, particularly those with highly active RA, have a high risk for development of lymphoma because of the RA in and of itself. Although there has been no increase in the rate or type of malignancies, there may be an increased risk for development of lymphoma in the patient population

who has been treated with TNF $\alpha$  inhibitor therapy. Thus, an increased risk of malignancy with chronic long-term TNF $\alpha$  inhibition and, specifically, the development of lymphoma are included in the BOXED WARNING section for anti-TNF $\alpha$  inhibitors.

Other known safety concerns for anti-TNF $\alpha$  inhibitors include anaphylaxis or allergic reactions, demyelinating disease, cytopenias/pancytopenias, heart failure, and lupus-like syndrome. Injection site reactions represent the most frequent and consistent side effect with administration of anti-TNF $\alpha$  therapy. These reactions tend to occur early after initiation of treatment and are generally mild and self-limited.

### 7.3 Major Safety Results

Through the 24-week Double-Blind Treatment Period, the general number of AEs is similar across treatment arms. Table 31 is a summary of the major safety findings in PsA001. There were more serious AEs and discontinuations from AEs in the CZP-treated subjects, but the numbers were low and similar to that in the placebo arm. There were 2 deaths during the 24-week Double-Blind period, and both deaths occurred in the CZP-treatment arms. A more detailed discussion of all of these findings will follow in the sections below.

**Table 31. Summary of Adverse Events**

<b>Summary of Adverse Events during Double-Blind Treatment Period</b>				
<b>System Organ Class/ Preferred Term</b>	<b>PBO<sup>a</sup></b>	<b>CZP 200mg q2w</b>	<b>CZP 400mg q4w</b>	<b>All CZP<sup>b</sup></b>
	<b>N=136 n (%)</b>	<b>N=138 n(%)</b>	<b>N=135 n(%)</b>	<b>N=332 n(%)</b>
<b>Any TEAEs</b>	92 (67.6)	94 (68.1)	96 (71.1)	207 (62.3)
<b>TEAEs by intensity:</b>				
Mild	74 (54.4)	78 (56.5)	77 (57.0)	168 (50.6)
Moderate	49 (36.0)	47 (34.1)	45 (33.3)	99 (29.8)
Severe	2 (1.5)	7 (5.1)	7 (5.2)	15 (4.5)
<b>Serious TEAEs</b>	6 (4.4)	8 (5.8)	13 (9.6)	22 (6.6)
<b>Discontinuation due to TEAEs:</b>				
Permanent discontinuation	2 (1.5)	4 (2.9)	6 (4.4)	10 (3.0)
Temporary discontinuation	19 (14.0)	30 (21.7)	25 (18.5)	56 (16.9)
<b>Death</b>	-	1 (0.7)	1 (0.7)	2 (0.6)

a For the entire PBO group, CZP data from PBO subjects were not utilized.

b The All CZP column includes CZP 200mg q2w, CZP 400mg q4w, and escaped PBO subjects with CZP data. Source: PsA001 Summary of Clinical Safety, Table 2\_1, page 49.

### 7.3.1 Deaths

Two deaths were reported in the Double-Blind Treatment period. Four additional deaths occurred through the data cutoff date of 31 May 2012; these subjects were in the Dose-Blind or Open-Label Treatment Periods. Six deaths occurred among 393 patients contributing 458.7 CZP person-years at risk; thus, the event-rate is 1.3 deaths per 100-patient years. This seems to be comparable to that seen in other anti-TNF $\alpha$  medications.

Table 32 further describes the causes of these 6 deaths along with the timing of the death to CZP exposure. For most of these deaths, the subjects had other medical conditions that could have contributed to their death. Table 33 provides the narratives for the 6 deaths. Overall, the types of deaths are consistent with what has been seen with other anti-TNF $\alpha$  medications.

**Table 32. Summary of Deaths in PsA001**

Case id/ Subject id	Treatment group	Age at death (years)	Gender	Country	SAE preferred term	First CZP dose/Last CZP dose	Duration of exposure (days)	Date of death	Causality assessment Investigator/ Sponsor
(b) (6)	CZP 400mg Q4W	43	F	Czech Republic	Sudden Death	(b) (6)	56	(b) (6)	Unrelated/ related
	CZP 200mg Q2W	50	M	US	Cardiac Arrest		70		Unrelated/ unrelated
	CZP 200mg Q2W	66	F	Poland	Breast Cancer		346		Related/ related
	PBO till wk24 for Q4W	70	F	US	Lymphoma		281		Related/ related
	PBO till wk 16 for Q2W	53	M	Poland	Cardiac Infarction		362		Unrelated/ unrelated
	CZP 400mg Q4W for 54wk	61	M	Argentina	Sepsis		365		Related/ related

<sup>a</sup> When date of death is missing, the first date of the month will apply

CZP-certolizumab pegol, PBO-placebo, SAE-severe adverse event, Q2W=every 2 weeks, Q4W-every 4 weeks

Source: PsA001 Mortality Report, Table 5.1, page 1

**Table 33. Narratives of Six Deaths in PsA001 through Data Cutoff Date (31 May 2012)**

Subject #	Narrative
<b>Double-Blind Treatment Period</b>	
1	<p>(b) (6)</p> <p><b>50-year-old white male (USA)</b> had a past medical history of psoriasis and PsA. His medications included methotrexate, folic acid, celecoxib, acet/salicylic acid, and cetyl alcohol. He was first exposed to CZP 200mg q2wks on (b) (6), and he received his last dose on (b) (6). On the day of his death (4 days after his last injection), he went for a jog and, apparently, collapsed about 15 minutes later. By the time EMS arrived, he was in asystole. Autopsy report revealed atherosclerotic heart disease with 80-85% stenosis in the left anterior descending artery and 75-80% in the right coronary arteries. Thus, cause of death was deemed to be <b>cardiac arrest</b> secondary to atherosclerotic cardiovascular disease.</p>

2	(b) (6)	<p><b>42 year-old white female</b> (Czech Republic) had a past medical history of PsA and hypertension. Her concomitant medications included celecoxib, methylprednisolone acetate, methotrexate, amiloride hydrochloride+chlorthalidone and betaxolol hydrochloride, folic acid, potassium, calcium, and Cilest (ethinylestradiol and norgestimate). She was enrolled in the CZP 400mg q4w study group and received her first injection on (b) (6). Her last scheduled dose was (b) (6). Four days after her last injection, she was reported to have died from <b>sudden death</b>. An autopsy was performed without clear diagnosis. Of note, at the time of her last injection (b) (6), she was noted to have a low potassium level (3.3 mmol/L); it is unclear if this could have been a signal of something else or could have contributed to her death.</p>
<b>Dose-Blind or Open-Label Treatment Period (through data cutoff date 31 May 2012)</b>		
3	(b) (6)	<p><b>66-year-old white female</b> (Poland) had a medical history significant for PsA, hypertension, and hypothyroidism. Her concomitant medications included omeprazole, ramipril, levothyroxine sodium, folic acid, bisoprolol, methotrexate, and diclofenac. She was in the CZP 200mg q2w study arm and received her first dose of medication on (b) (6). During the Dose-Blind Treatment period (specifically, (b) (6)) she presented to the hospital with dyspnea. Eventually, she was diagnosed with <b>breast cancer</b> (b) (6). Treatment with CZP was discontinued. She subsequently received oncologic treatment and died (b) (6). UCB was unable to obtain any more information about her death from her family.</p>
4	(b) (6)	<p><b>59-year-old white male</b> (Argentina) had a medical history notable for PsA and current tobacco use. His other medications included meloxicam, glucosamine, and carbamazepine. He had received CZP 400mg q4w in the Double-Blind, Dose-Blind, and Open-Label Treatment Periods of study PsA001. He was hospitalized on (b) (6) (approximately 54 weeks after initiation of study treatment) for <b>pneumonia</b>. Study drug was stopped on (b) (6). On (b) (6), his condition worsened with the development of <b>sepsis</b> and requirement for mechanical ventilation. His pneumonia continued to worsen with imaging revealing bilateral interstitial involvement and sputum revealing <i>Klebsiella pneumoniae</i> and <i>Pseudomonas aeruginosa</i>. He died on (b) (6).</p>
5	(b) (6)	<p><b>69-year-old white female</b> (USA) had an extensive medical history including PsA, hypertension, dyslipidemia, diabetes mellitus type 2, chronic asthma, cholelithiasis, benign breast mass, and allergy to IV dye. Her family history was significant for breast cancer (mother) and colon cancer (uncle). Her medication list was also extensive and included methotrexate, glimepiride, hydrochlorothiazide and triamterine, atenolol, omeprazole, simvastatin, cyclobenzaprine, salbutamol, omeprazole, alprazolam, oxycodone-acetaminophen, fluticasone propionate, and folic acid. She received placebo during the Double-Blind portion of the study ( (b) (6) ), and she crossed over to the CZP 400mg arm on (b) (6). Her last dose of medication was (b) (6). In (b) (6) (after approximately 67 weeks of study treatment), she was hospitalized for a UTI (<i>Klebsiella pneumoniae</i>). This hospitalization led to diagnosis of aggressive <b>lymphoma</b> with imaging showing extensive upper abdominal lymphadenopathy and splenomegaly. She was treated with high dose steroids and rituximab. This subject died on (b) (6).</p>
6	(b) (6)	<p><b>52-year-old white male</b> (Poland) had a past medical history notable for HTN, dyslipidemia, and PsA. His concomitant medications included methotrexate, ketoprofen, methylprednisolone, folic acid, enalapril maleate, indapamide, and simvastatin. He was enrolled in PsA and was originally randomized in the placebo arm. He escaped at Week 16 to the CZP 200mg q2w treatment arm and continued to receive this dose through the Dose-Blind and Open-Label Treatment Periods. He died on (b) (6) from acute left ventricular heart failure secondary to <b>septal myocardial infarction</b>. Autopsy showed evidence of chronic myocardial ischemia with an old infarct to the left ventricle.</p>

Source: Summary of Clinical Efficacy, pages 70-72; PsA001 Mortality Report, Section 5.1, pages 12-16.

### 7.3.2 Nonfatal Serious Adverse Events

Table 34 presents the non-fatal SAEs during the Double-Blind Treatment Period (Week 24). Overall, the proportion of subjects with SAEs was similar between the placebo and all CZP groups. When analyzing the two CZP groups separately, there was a slightly higher proportion in the CZP 400mg q4w treatment arm. The most common SOC for the CZP groups was Infections and Infestations.

**Table 34. Summary of Non-Fatal SAEs During Double-Blind Treatment Period of PsA001**

Summary of Non-Fatal SAEs during Double-Blind Treatment Period				
System Organ Class/ Preferred Term	PBO <sup>a</sup>  N=136 n (%)	CZP 200mg q2w  N=138 n(%)	CZP 400mg q4w  N=135 n(%)	All CZP <sup>b</sup>  N=332 n(%)
<b>Any Non-fatal SAE</b>	<b>6 (4.4)</b>	<b>7 (5.1)</b>	<b>12 (8.9)</b>	<b>20 (6.0)</b>
<b>Cardiac disorders</b>	-	1 (0.7)	1 (0.7)	2 (0.6)
Acute myocardial infarction	-	1 (0.7)	-	1 (0.3)
Angina unstable	-	-	1 (0.7)	1 (0.3)
<b>Ear and labyrinth disorders</b>	-	-	1 (0.7)	1 (0.3)
Tinnitus	-	-	1 (0.7)	1 (0.3)
<b>Gastrointestinal disorders</b>	-	1 (0.7)	-	1 (0.3)
Abdominal hernia	-	1 (0.7)	-	1 (0.3)
<b>General disorders and administration site conditions</b>	1 (0.7)	-	-	-
Chest pain	1 (0.7)	-	-	-
<b>Infections and infestations</b>	1 (0.7)	2 (1.4)	2 (1.5)	4 (1.2)
Herpes Zoster	-	1 (0.7)	-	1 (0.3)
Bronchitis	-	-	1 (0.7)	1 (0.3)
Bronchopneumonia	-	1 (0.7)	-	1 (0.3)
Pneumonia	-	-	1 (0.7)	1 (0.3)
Pyelonephritis	1 (0.7)	-	-	-
<b>Injury, poisoning, and procedural complications</b>	2 (1.5)	-	1 (0.7)	2 (0.6)
Concussion	-	-	1 (0.7)	1 (0.3)
Heat exhaustion	1 (0.7)	-	-	-
Tendon rupture	1 (0.7)	-	-	1 (0.3)
<b>Investigations</b>	-	1 (0.7)	-	1 (0.3)
Hepatic enzyme increased	-	1 (0.7)	-	1 (0.3)
<b>Metabolism and nutrition disorders</b>	-	-	2 (1.5)	2 (0.6)
Diabetes mellitus	-	-	1 (0.7)	1 (0.3)
Obesity	-	-	1 (0.7)	1 (0.7)
<b>Musculoskeletal and connective tissue disorder</b>	-	-	2 (1.5)	2 (0.6)
Osteoarthritis	-	-	1 (0.7)	1 (0.3)
Psoriatic arthropathy	-	-	1 (0.7)	1 (0.3)
<b>Nervous system disorders</b>	-	-	1 (0.7)	1 (0.3)
Cerebrovascular accident	-	-	1 (0.7)	1 (0.3)
<b>Pregnancy, puerperium, and perinatal conditions</b>	-	-	1 (0.7)	1 (0.3)
Pregnancy	-	-	1 (0.7)	1 (0.3)
<b>Renal and urinary disorders</b>	1 (0.7)	-	-	-
Nephrolithiasis	1 (0.7)	-	-	-
<b>Reproductive system and breast disorders</b>	-	1 (0.7)	-	1 (0.3)
Vulvar dysplasia	-	1 (0.7)	-	1 (0.3)
<b>Respiratory, thoracic, and</b>	-	1 (0.7)	-	1 (0.3)

<b>mediastinal disorders</b>				
Pleurisy	-	1 (0.7)	-	1 (0.3)
<b>Skin and subcutaneous tissue disorders</b>	-	1 (0.7)	-	1 (0.3)
Cutaneous lupus erythematosus	-	1 (0.7)	-	1 (0.3)
<b>Social circumstances</b>	-	-	1 (0.7)	1 (0.3)
Pregnancy of partner	-	-	1 (0.7)	1 (0.3)
<b>Surgical and medical procedures</b>	1 (0.7)	-	-	-
Hospitalization	1 (0.7)	-	-	-
<b>Vascular disorders</b>	1 (0.7)	-	-	-
Hypertension	1 (0.7)	-	-	-

a For the entire PBO group, CZP data from PBO subjects were not utilized.

b The All CZP column includes CZP 200mg q2w, CZP 400mg q4w, and escaped PBO subjects with CZP data.

Source: PsA001 Summary of Clinical Safety, Table 2\_9, pages 73-75.

Table 35 is an exposure-adjusted summary of nonfatal serious adverse events (SAEs). As already described, the Double-Blind Safety Pool includes any subject who received CZP during the Double-Blind Treatment Period, whereas the All CZP Safety Pool includes all subjects who received CZP through the data cutoff data of 31 May 2012. The exposure-adjusted incidence rate was calculated for these time periods. In the Double-Blind Safety Pool, it appears that CZP 400mg treatment arm (20.92/100 pt-yrs) has a higher incidence rate as compared to placebo (11.74/100 pt-yrs) and CZP 200mg (10.72/100 pt-yrs). However, with longer exposure, the incidence rate in the CZP 400mg treatment arm is actually lower (11.84/100 pt-yrs) and more similar to CZP 200mg (9.98/100 pt-yrs). The exposure-adjusted incidence rate in the CZP 400mg group at data cutoff is even closer to the placebo incidence rate during the double-blind period. In this exposure-adjusted analysis, Infections and Infestations remains the most common SOC. The incidence rate remained similar (to lower) in the CZP treatment arms even after longer exposure. The next most common SOC in the CZP treatment arms was Musculoskeletal and Connective Tissue Disorders under which the most common PT was persistent symptoms from PsA.

**Table 35. Exposure-Adjusted Summary of Non-fatal SAEs in PsA001**

System Organ Class/ Preferred Term	Double Blind Safety Pool (0-24 wks)			All CZP Safety Pool (data cut-off 31 May 2012)	
	PBO N = 136	CZP 200mg q2wks N = 169	CZP 400mg q4wks N = 165	CZP 200mg q2wks N = 197	CZP 400mg q4wks N = 196
Patient exposure years	51.1	66.9	64.6	232.4	226.3
Any Nonfatal SAEs n/# (IR)	6/7 (11.74)	7/8 (10.72)	13/13 (20.92)	22/29 (9.98)	25/35 (11.84)
<b>System Organ Class and Preferred Term n/# of events (incidence per 100 patient-years)</b>					
<b>Cardiac disorders</b>	-	1/1 (1.50)	1/1 (1.56)	4/4 (1.74)	1/1 (0.44)
Angina unstable	-	-	1/1 (1.56)	1/1 (0.43)	1/1 (0.44)
Acute myocardial infarction	-	1/1 (1.50)	-	1/1 (0.43)	-
Myocardial infarction	-	-	-	1/1 (0.43)	-
Myocarditis	-	-	-	1/1 (0.43)	-
<b>Ear and labyrinth disorders</b>	-	-	1/1 (1.55)	-	1/1 (0.44)
Tinnitus	-	-	1/1 (1.55)	-	1/1 (0.44)
<b>Gastrointestinal disorders</b>	-	1/1 (1.50)	-	2/2 (0.87)	-
Abdominal hernia	-	1/1 (1.50)	-	1/1 (0.43)	-
Umbilical hernia	-	-	-	1/1 (0.43)	-
<b>General disorders and administration site conditions</b>	1/1 (2.0)	-	-	1/1 (0.43)	1/1 (0.44)
Pyrexia	-	-	-	-	1/1 (0.44)
Chest pain	1/1 (2.0)	-	-	1/1 (0.43)	-
<b>Hepatobiliary disorders</b>	-	-	-	-	1/1 (0.44)
Biliary dyskinesia	-	-	-	-	1/1 (0.44)
<b>Infections and infestations</b>	1/1 (2.0)	2/2 (3.01)	2/2 (3.11)	4/4 (1.74)	6/9 (2.65)
Arthritis bacterial	-	-	-	-	1/1 (0.44)
Cellulitis	-	-	-	1/1 (0.43)	-
Herpes Zoster	-	1/1 (1.50)	-	1/1 (0.43)	-
Pneumonia	-	-	1/1 (1.55)	-	2/3 (0.88)
Bronchitis	-	-	1/1 (1.55)	-	1/1 (0.44)
Bronchopneumonia	-	1/1 (1.50)	-	1/1 (0.43)	-
HIV infection	-	-	-	1/1 (0.43)	1/1 (0.44)

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Latent tuberculosis	-	-	-	-	1/1 (0.44)
Upper respiratory tract infection	-	-	-	-	1/1 (0.44)
Urinary tract infection	-	-	-	-	1/1 (0.44)
Pyelonephritis	1/1 (2.0)	-	-	-	-
<b>Injury, poisoning, and procedural complications</b>	2/2 (3.9)	-	2/2 (3.11)	3/4 (1.30)	4/5 (1.80)
Concussion	-	-	1/1 (1.55)	-	1/1 (0.44)
Joint injury	-	-	-	1/1 (0.43)	-
Synovial rupture	-	-	-	-	1/1 (0.44)
Foot fracture	-	-	-	-	1/1 (0.44)
Tendon rupture	1/1 (2.0)	-	1/1 (1.55)	-	2/2 (0.89)
Animal bite	-	-	-	1/1 (0.43)	-
Wound	-	-	-	1/1 (0.43)	-
Hand fracture	-	-	-	1/1 (0.43)	-
Heat exhaustion	1/1 (2.0)	-	-	-	-
<b>Investigations</b>	-	1/1 (1.50)	-	1/1 (0.43)	-
Hepatic enzyme increased	-	1/1 (1.50)	-	1/1 (0.43)	-
<b>Metabolism and nutrition disorders</b>	-	-	2/2 (3.11)	1/1 (0.43)	2/2 (0.89)
Diabetes mellitus	-	-	1/1 (1.55)	-	1/1 (0.44)
Obesity	-	-	1/1 (1.55)	-	1/1 (0.44)
Dehydration	-	-	-	1/1 (0.43)	-
<b>Musculoskeletal and connective tissue disorder</b>	-	-	2/2 (3.12)	2/2 (0.86)	5/6 (2.24)
Foot deformity	-	-	-	-	1/1 (0.44)
Osteoarthritis	-	-	1/1 (1.55)	-	1/1 (0.45)
Psoriatic arthropathy	-	-	1/1 (1.55)	2/2 (0.86)	3/4 (1.33)
<b>Neoplasms benign, malignant, and unspecified</b>	-	-	-	-	1/1 (0.44)
Breast cancer	-	-	-	-	1/1 (0.44)
<b>Nervous system disorders</b>	-	-	1/1 (1.55)	1/1 (0.43)	3/3 (1.33)
Cerebrovascular accident	-	-	1/1 (1.55)	-	1/1 (0.44)
Syncope	-	-	-	-	1/1 (0.44)
Paralysis	-	-	-	1/1 (0.43)	-
Transient ischemic attack	-	-	-	-	1/1 (0.44)

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<b>Pregnancy, pueriperium, and perinatal conditions</b>	-	-	1/1 (1.55)	-	1/1 (0.44)
Pregnancy	-	-	1/1 (1.55)	-	1/1 (0.44)
<b>Renal and urinary disorders</b>	1/1 (2.0)	-	-	-	-
Nephrolithiasis	1/1 (2.0)	-	-	-	-
<b>Reproductive system and breast disorders</b>	-	1/1 (1.50)	-	2/2 (0.87)	2/2 (0.89)
Metrorrhagia	-	-	-	1/1 (0.43)	-
Genital prolapse	-	-	-	-	1/1 (0.44)
Uterine polyp	-	-	-	-	1/1 (0.44)
Vulvar dysplasias	-	1/1 (1.50)	-	1/1 (0.43)	-
<b>Respiratory, thoracic, and mediastinal disorders</b>	-	1/1 (1.50)	-	3/3 (1.29)	-
Dyspnea	-	-	-	1/1 (0.43)	-
Pleurisy	-	1/1 (1.50)	-	1/1 (0.43)	-
Pulmonary embolism	-	-	-	1/1 (0.43)	-
<b>Skin and subcutaneous tissue disorders</b>	-	1/1 (1.50)	-	1/2 (0.43)	-
Cutaneous lupus erythematosus	-	1/1 (1.50)	-	1/2 (0.43)	-
<b>Social circumstances</b>	-	-	1/1 (1.55)	-	1/1 (0.44)
Pregnancy of partner	-	-	1/1 (1.55)	-	1/1 (0.44)
<b>Surgical and medical procedures</b>	1/1 (2.0)	-	-	-	1/1 (0.44)
Hip arthroplasty	-	-	-	-	1/1 (0.44)
Hospitalization	1/1 (2.0)	-	-	-	-
<b>UNCODED</b>	-	-	-	-	1/1 (0.44)
<b>Vascular disorders</b>	1/1 (2.0)	-	-	2/2 (0.86)	-
Hypertension	1/1 (2.0)	-	-	-	-
Venous thrombosis	-	-	-	1/1 (0.43)	-
Deep vein thrombosis	-	-	-	1/1 (0.43)	-

Source: PSA001 Clinical Safety Global Tables, Table 8.11:2, pages 1263-1297

### 7.3.3 Dropouts and/or Discontinuations

In the 24-week Double-Blind Treatment Period, the number of adverse events leading to discontinuation was low. Table 36 summarizes the adverse events in the PBO and CZP treatment arms. Overall, these were individual events without a predominant PT or SOC.

**Table 36. Summary of AEs Leading to Discontinuation During 24-wk Double-Blind Treatment Period**

<b>Summary of AEs Leading to Discontinuation during Double-Blind Treatment Period</b>				
<b>System Organ Class/ Preferred Term</b>	<b>PBO<sup>a</sup></b>	<b>CZP 200mg q2w</b>	<b>CZP 400mg q4w</b>	<b>All CZP<sup>b</sup></b>
	<b>N=136 n (%)</b>	<b>N=138 n(%)</b>	<b>N=135 n(%)</b>	<b>N=332 n(%)</b>
<b>Any AE leading to discontinuation</b>	<b>2 (1.5)</b>	<b>4 (2.9)</b>	<b>6 (4.4)</b>	<b>10 (3.0)</b>
<b>Cardiac disorders</b>	-	1 (0.7)	-	1 (0.3)
Cardiac arrest	-	1 (0.7)	-	1 (0.3)
<b>General disorders and administration site conditions</b>	-	-	1 (0.7)	1 (0.3)
Sudden death	-	-	1 (0.7)	1 (0.3)
<b>Immune system disorders</b>	1 (0.7)	-	-	-
Allergic edema	1 (0.7)	-	-	-
<b>Infections and infestations</b>	-	-	1 (0.7)	1 (0.7)
Sinusitis	-	-	1 (0.7)	1 (0.7)
<b>Investigations</b>	-	2 (1.4)	-	2 (0.6)
Alanine aminotransferase increased	-	1 (0.7)	-	1 (0.3)
Aspartate aminotransferase increased	-	1 (0.7)	-	1 (0.3)
Hepatic enzyme increased	-	1 (0.7)	-	1 (0.3)
<b>Musculoskeletal and connective tissue disorder</b>	-	-	1 (0.7)	1 (0.3)
Psoriatic arthropathy	-	-	1 (0.7)	1 (0.3)
<b>Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)</b>	-	-	1 (0.7)	1 (0.3)
Cervix carcinoma stage 0	-	-	1 (0.7)	1 (0.3)
<b>Nervous system disorders</b>	-	-	1 (0.7)	1 (0.3)
Cerebrovascular accident	-	-	1 (0.7)	1 (0.3)
<b>Pregnancy, puerperium, and perinatal conditions</b>	-	-	1 (0.7)	1 (0.3)
Pregnancy	-	-	1 (0.7)	1 (0.3)
<b>Respiratory, thoracic, and mediastinal disorders</b>	1 (0.7)	1 (0.7)	-	1 (0.3)
Dyspnea	1 (0.7)	-	-	-
Pleurisy	-	1 (0.7)	-	1 (0.3)

a For the entire PBO group, CZP data from PBO subjects were not utilized.

b The All CZP column includes CZP 200mg q2w, CZP 400mg q4w, and escaped PBO subjects with CZP data.

Source: PsA001 Summary of Clinical Safety, Table 2\_11, pages 81-82.

Table 37 is an exposure-adjusted summary of the same information -- AEs leading to discontinuation. Overall, the exposure-adjusted incidence rate is higher in the CZP-treated groups than placebo in the Double-Blind Treatment Period. Like the SAEs described earlier, it appears that there is a higher incidence rate in subjects who received CZP 400mg. However, with longer exposure, the incidence rate again decreases and becomes more comparable to the CZP 200mg treatment arm (6.68/100 pt-yrs in the CZP 400mg group vs. 6.53/100 pt-years in the CZP 200mg group). Again, the Infection and Infestations SOC had the most AEs leading to discontinuation. The second most common SOC was the Investigations, particularly in the CZP 200mg treatment arm.

**Table 37. Exposure-Adjusted Summary of AEs Leading to Discontinuation**

System Organ Class/ Preferred Term	Double Blind Safety Pool (0-24 wks)			All CZP Safety Pool (data cut-off 31 May 2012)	
	PBO N = 136	CZP 200mg q2wks N = 169	CZP 400mg q4wks N = 165	CZP 200mg q2wks N=197	CZP 400mg q4wks N=196
Patient exposure years	51.1	66.9	64.6	232.4	226.3
Any AE leading to discontinuation n/# (IR)	2/2(3.91)	3/4 (4.51)	6/6 (9.37)	15/21 (6.53)	15/15 (6.68)
System Organ Class and Preferred Term n/# of events (incidence per 100 patient-years)					
<b>Cardiac disorders</b>	-	-	-	1/1 (0.43)	-
Myocarditis	-	-	-	1/1 (0.43)	-
<b>Eye disorders</b>	-	-	-	2/3 (0.86)	-
Lacrimation increased	-	-	-	1/1 (0.43)	-
Periorbital edema	-	-	-	1/1 (0.43)	-
Ocular hyperemia	-	-	-	1/1 (0.43)	-
<b>General disorders and administration site conditions</b>	-	-	1/1 (1.55)	-	1/1 (0.44)
Sudden death	-	-	1/1 (1.55)	-	1/1 (0.44)
<b>Immune system disorders</b>	1/1 (0.7)	-	-	-	-
Allergic edema	1/1 (0.7)	-	-	-	-
<b>Infections and infestations</b>	-	-	1/1 (1.55)	3/3 (1.29)	7/7 (3.10)
Pneumonia	-	-	-	-	1.1 (0.44)
HIV infection	-	-	-	1/1 (0.44)	1/1 (0.44)
Subcutaneous abscess	-	-	-	-	1/1 (0.44)

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Tuberculosis	-	-	-	2/2 (0.86)	1/1 (0.44)
Latent TB	-	-	-	-	2/2 (0.88)
Sinusitis	-	-	1/1 (1.55)	-	1/1 (0.44)
<b>Investigations</b>	-	2/3 (3.00)	-	4/5 (1.73)	1/1 (0.44)
Alanine aminotransferase increased	-	1.1 (1.50)	-	2/2 (0.86)	-
Aspartate aminotransferase increased	-	1/1 (1.50)	-	1/1 (0.43)	-
Hepatic enzyme increased	-	1/1 (1.50)	-	1/1 (0.43)	-
Tuberculin test positive	-	-	-	1/1 (0.43)	1/1 (0.44)
<b>Musculoskeletal and connective tissue disorder</b>	-	-	1/1 (1.55)	-	2/2 (0.89)
Psoriatic arthropathy	-	-	1/1 (1.55)	-	2/2 (0.89)
<b>Neoplasms benign, malignant, and unspecified</b>	-	-	1/1 (1.55)	1/1 (0.43)	2/2 (0.88)
Breast cancer	-	-	-	1/1 (0.43)	-
Cervix carcinoma stage 0	-	-	1/1 (1.55)	-	1/1 (0.44)
Lymphoma	-	-	-	-	1/1 (0.44)
<b>Nervous system disorders</b>	-	-	1/1 (1.55)	-	1/1 (0.44)
Cerebrovascular accident	-	-	1/1 (1.55)	-	1/1 (0.44)
<b>Pregnancy, pueriperium, and perinatal conditions</b>	-	-	1/1 (1.55)	-	1/1 (0.44)
Pregnancy	-	-	1/1 (1.55)	-	1/1 (0.44)
<b>Respiratory, thoracic, and mediastinal disorders</b>	1/1 (0.7)	1/1 (1.50)	-	1/1 (0.43)	-
Dyspnea	1/1 (0.7)	-	-	-	-
Pleurisy	-	1/1 (1.50)	-	1/1 (0.43)	-
<b>Skin and subcutaneous tissue disorders</b>	-	-	-	4/4 (1.73)	-
Cutaneous lupus erythematosus	-	-	-	1/1 (0.43)	-
Dermatitis allergic	-	-	-	1/1 (0.43)	-
Psoriasis	-	-	-	2/2 (0.86)	-
<b>UNCODED</b>	-	-	-	1/3 (0.43)	-

Source: PSA001 Safety Pooling (data cutoff 31 May 2012), pages 1297-1314.

### 7.3.4 Significant Adverse Events

Adverse events of special interest for TNF $\alpha$ -inhibitors are discussed below in Section 7.3.5. AEs leading to discontinuation were previously discussed in Section 7.3.3.

### 7.3.5 Submission Specific Primary Safety Concerns

TNF $\alpha$ -inhibitors, as a class of medication, have a well-characterized safety profile as described in Section 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class. Thus, because of the known safety profile of anti-TNF $\alpha$  therapy, the following categories of adverse events – infections, malignancy, cardiovascular events, hypersensitivity reactions, and neurologic events – are adverse events of interest.

#### *Infections*

Overall, the number of infections is similar across treatment arms. Table 38 presents the number of events in the Infections and Infestations SOC during the 24-week Double-Week Treatment Period. In addition, Table 38 shows the number of events within the Infection SOC that were considered severe and serious and that led to drug discontinuation. Again, the numbers are quite similar across treatment arms.

**Table 38. Summary of AEs in the Infections and Infestations SOC**

Summary of Infections during Double-Blind Treatment Period				
Infections and infestations SOC	PBO <sup>a</sup>	CZP 200mg q2w	CZP 400mg q4w	All CZP <sup>b</sup>
	N=136 n (%)	N=138 n (%)	N=135 n (%)	N=332 n (%)
Any AEs n(%)	52 (38.2)	60 (43.5)	54 (40.0)	119 (35.8)
Severe TEAEs	-	1 (0.7)	1 (0.7)	2 (0.6)
Drug-related TEAEs	20 (14.7)	18 (13.0)	19 (14.1)	37 (11.1)
Serious TEAEs	1 (0.7)	2 (1.4)	2 (1.5)	4 (1.2)
Discontinuations due to TEAEs:				
Permanent discontinuation	-	-	1 (0.7)	1 (0.3)
Temporary discontinuation	12 (8.8)	19 (13.8)	15 (11.1)	35 (10.5)
Death	-	-	-	-

<sup>a</sup> For the entire PBO group, CZP data from PBO subjects were not utilized.

<sup>b</sup> The All CZP column includes CZP 200mg q2w, CZP 400mg q4w, and escaped PBO subjects with CZP data.

Source: PsA001 Summary of Clinical Safety, Table 2\_13, page 89.

Table 39 further details the most common PTs within the Infection and Infestations SOC. In the CZP-exposed treatment arms, the most common PTs

were nasopharyngitis, upper respiratory infection, and sinusitis – all within the Upper Respiratory Infection HLT (high level term).

**Table 39. Summary of Common PTs (≥1.5%) in the Infections and Infestations SOC in the Double-Blind Treatment Period (Wks 0-24)**

Summary of Common Infections during Double-Blind Treatment Period				
High Level Term/ Preferred Term	PBO <sup>a</sup>	CZP 200mg q2w	CZP 400mg q4w	All CZP <sup>b</sup>
	N=136 n (%)	N=138 n(%)	N=135 n(%)	N=332 n(%)
<b>Any infections n(%)# of events</b>	52 (38.2)/68	60 (43.5)/97	54 (40.0)/81	119 (35.8)/184
<b>Bacterial infections NEC</b>	-	2 (1.4)	3 (2.2)	5 (1.5)
Cellulitis	-	1 (0.7)	2 (1.5)	3 (0.9)
<b>Dental and oral soft tissue infections</b>	3 (2.2)	-	-	-
Tooth abscess	2 (1.5)	-	-	-
<b>Fungal infections NEC</b>	-	2 (1.4)	2 (1.5)	4 (1.2)
Vulvovaginal mycotic infections	-	1 (0.7)	2 (1.5)	3 (0.9)
<b>Herpes viral infection</b>	3 (2.2)	4 (2.9)	7 (5.2)	12 (3.6)
Oral herpes	3 (2.2)	2 (1.4)	4 (3.0)	7 (2.1)
<b>Infections NEC</b>	2 (1.5)	3 (2.2)	2 (1.5)	6 (1.8)
Respiratory tract infection	2 (1.5)	1 (0.7)	1 (0.7)	3 (0.9)
<b>Influenza virus infection</b>	2 (1.5)	2 (1.4)	3 (2.2)	5 (1.5)
Influenza	2 (1.5)	2 (1.4)	3 (2.2)	5 (1.5)
<b>Lower respiratory tract and lung infections</b>	7 (5.1)	7 (5.1)	7 (5.2)	14 (4.2)
Bronchitis	6 (4.4)	4 (2.9)	4 (3.0)	8 (2.4)
Pneumonia	-	2 (1.4)	2 (1.5)	4 (1.2)
<b>Upper respiratory tract infections</b>	21 (15.4)	38 (27.5)	38 (28.1)	79 (23.8)
Nasopharyngitis	10 (7.4)	18 (13.0)	9 (6.7)	29 (8.7)
Upper respiratory tract infection	7 (5.1)	12 (8.7)	13 (9.6)	26 (7.8)
Pharyngitis	3 (2.2)	6 (4.3)	4 (3.0)	10 (3.0)
Sinusitis	1 (0.7)	3 (2.2)	6 (4.4)	9 (2.7)
Acute sinusitis	-	2 (1.4)	2 (1.5)	4 (1.2)
Rhinitis	1 (0.7)	3 (2.2)	1 (0.7)	4 (1.2)
<b>Urinary tract infections</b>	11 (8.1)	4 (2.9)	4 (3.0)	8 (2.4)
Urinary tract infection	9 (6.6)	3 (2.2)	4 (3.0)	7 (2.1)
<b>Viral infections NEC</b>	4 (2.9)	6 (4.3)	4 (3.0)	10 (3.0)
Viral infection	1 (0.7)	3 (2.2)	2 (1.5)	5 (1.5)
Gastrointestinal viral	2 (1.5)	1 (0.7)	2 (1.5)	3 (0.9)

a For the entire PBO group, CZP data from PBO subjects were not utilized.

b The All CZP column includes CZP 200mg q2w, CZP 400mg q4w, and escaped PBO subjects with CZP data.

Source: PSA001 Summary of Clinical Safety, Table 2-15, page 91.

PSA001 Tables, Table 8.2, pages 1138-1146

In an exposure-adjusted analysis, the incidence rate showed a slightly higher incidence in the CZP treated groups compared to placebo. However, with longer exposure, the incidence rate decreased in the CZP-treatment groups. For serious infections, through the data cutoff date, the incidence rate is low for both CZP 200mg and CZP 400mg. Numerically, the incidence rate is higher in the CZP 400mg group – 3.14/100 patient-years for CZP 400mg q4w versus 1.5/100 patient-years for CZP 200mg q2w.

**Table 40. Exposure-Adjusted Summary of AEs in the Infections and Infestations SOC**

System Organ Class/ Preferred Term	Double Blind Safety Pool (0-24 wks)			All CZP Safety Pool (data cut-off 31 May 2012)	
	PBO N = 136	CZP 200mg q2wks N = 169	CZP 400mg q4wks N = 165	CZP 200mg q2wks N=197	CZP 400mg q4wks N=196
Patient exposure years	51.1	66.9	64.6	232.4	226.3
n/# of events (incidence per 100 patient-years)					
Any TEAEs	52/68 (101.76)	64/103 (128.20)	57/85 (115.50)	114/248 (87.07)	103/228 (73.53)
Severe TEAEs	-	1/1	1/1	4/4	5/7
Drug-related TEAEs	20/22	18/33	21/31	44/80	50/94
Serious TEAEs	1/1 (1.96)	2/2 (3.01)	2/2 (3.11)	4/4 (1.74)	7/10 (3.14)
Permanent discontinuations due to TEAEs	-	-	1/1 (1.55)	3/3 (1.5)	7/7 (3.10)
Death	-	-	-	-	1/1 (0.44)

Source: PsA001 Summary of Clinical Safety, Table 2\_14, page 90.

Table 41 displays the serious infections that occurred in study PsA001. In the Double-Blind Treatment Period, there were a total of 4 serious infections in the CZP treatment arms (2 in each dose categories) and 1 serious infection in the placebo arm. There were an additional 10 serious infections in the CZP treated subjects through the data cutoff date. The most common serious infection was pneumonia. The second most common serious infection was HIV infection in 2 subjects treated with CZP. The other types of serious infections were single events.

**Table 41. Exposure-adjusted Summary of Serious Infections in PsA001**

System Organ Class/ Preferred Term	Double Blind Safety Pool (0-24 wks)			All CZP Safety Pool (data cut-off 31 May 2012)	
	PBO N = 136	CZP 200mg q2wks N = 169	CZP 400mg q4wks N = 165	CZP 200mg q2wks N=197	CZP 400mg q4wks N=196
Patient exposure years	51.1	66.9	64.6	232.4	226.3
All serious infections	1/1 (1.96)	2/2 (3.01)	2/2 (3.11)	4/4 (1.74)	7/10 (3.14)
n/# of events (incidence per 100 patient-years)					
Arthritis bacterial	-	-	-	-	1/1 (0.44)
Cellulitis	-	-	-	1/1 (0.43)	-
Herpes zoster	-	1/1 (1.50)	-	1/1 (0.43)	-
Pneumonia	-	-	1/1 (1.55)	-	2/3 (0.88)
Bronchitis	-	-	1/1 (1.55)	-	1/1 (0.44)
Bronchopneumonia	-	1/1 (1.50)	-	1/1 (0.43)	-
HIV infection	-	-	-	1/1 (0.43)	1/1 (0.44)
Sepsis	-	-	-	-	1/1 (0.44)
Latent tuberculosis	-	-	-	-	1/1 (0.44)
Upper respiratory tract infection	-	-	-	-	1/1 (0.44)
Urinary tract infection	-	-	-	-	1/1 (0.44)
Pyelonephritis	1/1 (1.96)	-	-	-	-

Source: PSA001 clinical safety global tables, Table 8.11:2, pages 1270-1276.

There were no cases of opportunistic infections during the 24-week Double-Blind Treatment Period. However, there were 3 opportunistic infections through the data cutoff date. As already mentioned, there were 2 cases of HIV, and there was also 1 nonserious case of ophthalmic herpes.

- SAE of HIV infection: Subject (b) (6) was a 30-year-old male in the CZP 400mg q4w group who was diagnosed with HIV during the Dose-Blind Treatment Period. His diagnosis was made after 268 days on study treatment. The study medication was discontinued as a result of his diagnosis.

- SAE of HIV infection: Subject [REDACTED] <sup>(b) (6)</sup> was a 37-year-old male who was initially randomized to placebo and crossed over to the CZP 200mg q2w group at Week 24. He was diagnosed during the Dose-Blind Treatment Period after 309 days on study treatment. The study medication was discontinued after his diagnosis.
- Nonserious AE of ophthalmic herpes infection: Subject [REDACTED] <sup>(b) (6)</sup> was a 40-year-old male in the CZP 400mg q4w group. He was also diagnosed during the Dose-Blind Treatment Period after 288 days on study treatment. The infection resolved after 15 days, and his medication was continued throughout its presence.

No events of TB occurred during the Double-Blind Treatment Period. However, through the data cutoff date, there were 8 cases of a positive PPD (which likely occurred at the Week 48 or Week 96 visit). After further evaluation, 3 of these cases were not felt to be active or latent TB. The other 5 cases were considered cases of latent TB although only one of these was counted as a SAE because that subject was hospitalized. Table 42 summarizes these cases of positive PPD.

**Table 42. Summary of Positive PPD Cases in PsA**

Site/subject number/region/age/gender	Preferred term (reported term)	SAE (Yes/No)	Treatment group	Days since 1 <sup>st</sup> CZP injection	Action taken; comments
(b) (6) East Europe/ 58/female	Tuberculin test positive (positive PPD skin test at Week 48)	No	Placebo escaping to CZP 200mg Q2W at Week 16	223	Drug permanently withdrawn; confirmed by query that there was no evidence of suspected latent or active TB
(b) (6) West Europe/ 50/female	Tuberculin test positive (positive Mantoux test [PPD])	No	Placebo escaping to CZP 400mg Q4W	225	Drug permanently withdrawn; no further information available regarding suspicion of latent TB
(b) (6) North America/ 73/female	Tuberculin test positive (positive PPD [tuberculin] test)	No	CZP 200mg Q2W	337	None; confirmed by query that there was no evidence of suspected latent or active TB
(b) (6) East Europe/ 35/female	Tuberculosis (suspected new latent or active TB)	No	CZP 200mg Q2W	340	Drug permanently withdrawn
(b) (6) East Europe/ 45/female	Tuberculosis (potential new latent or active TB)	No	CZP 200mg Q2W	337	Drug permanently withdrawn
(b) (6) Latin America/ 51/male	Tuberculosis (suspected new latent or active TB)	No	CZP 400mg Q4W	356	Drug permanently withdrawn
(b) (6) Latin America/ 30/female	Latent tuberculosis (suspected new latent TB)	Yes	Placebo throughout the DB to CZP 400mg Q4W	169	Drug permanently withdrawn
(b) (6) North America/ 42/female	Latent tuberculosis (latent tuberculosis)	No	Placebo escaping to CZP 400mg Q4W	549	Drug permanently withdrawn

Source: PSA001 Summary of Clinical Safety, Table 2-16, page 96.

*Malignancies*

Table 43 summarizes the cases of malignancy in the Double-Blind Treatment Period and the data cutoff date, by exposure. Within the Double-Blind period, the case involved a 31-year-old female who was diagnosed with cervical carcinoma (stage 0). Of note, there was another case (in a subject taking CZP 200mg q2w) of a “pre-malignant” case of vulvar dysplasia that was not included in this table. In addition, there was another subject in the placebo arm who developed breast cancer during the Double-Blind Period, but she was not included in the analysis because the event was reported after the database lock.

With greater exposure, there are numerically more events, but the incidence rate remains low and comparable to the 24-week Double Blind data. The cases of lymphoma and breast cancer (the one taking CZP 200mg) were ultimately fatal.

**Table 43. Exposure-adjusted Summary of Malignancies in PsA001**

System Organ Class/ Preferred Term	Double Blind Safety Pool (0-24 wks)			All CZP Safety Pool (data cut-off 31 May 2012)	
	PBO N = 136	CZP 200mg q2wks N = 169	CZP 400mg q4wks N = 165	CZP 200mg q2wks N=197	CZP 400mg q4wks N=196
Patient exposure years	51.1	66.9	64.6	232.4	226.3
All malignancies	-	-	1/1 (1.55)	2/2 (0.87)	3/3 (1.33)
n/# of events (incidence per 100 patient-years)					
Breast cancer	-	-	-	1/1 (0.43)	1/1 (0.44)
Cervix carcinoma stage 0	-	-	1/1 (1.55)	-	1 /1 (0.44)
Thyroid neoplasm	-	-	-	1/1 (0.43)	-
Lymphoma	-	-	-	-	1/1 (0.44)

Source: PSA001 Clinical Safety Global Tables, Table 8.11:5, pages 1361-1364.

Overall, the incidence of malignancies was similar to what has been seen with CZP and RA patients. In addition, these findings are consistent with other anti-TNFα medications.

### Cardiovascular (CV) events

The PsA population has an underlying increased risk for CV events. In addition, CV events, specifically congestive heart failure, have been described in subjects on anti-TNF $\alpha$  medications.

Table 44 summarizes the CV events in the 24-week Double-Blind Treatment Period. The number of events in the CZP-treated subjects (All CZP) is greater than in the placebo group. However, the most common CV event was hypertension with similar proportions in the placebo and CZP-treated groups. Table 44 highlights the serious CV events – acute myocardial infarction, unstable angina, cardiac arrest, sudden death, and cerebrovascular accident (CVA) – all of which occurred in CZP treated subjects. Two of these events were fatal and have previously been described.

**Table 44. Summary of Cardiovascular Events during the Double-Blind Treatment Period of PsA001**

Summary of Cardiovascular AEs during Double-Blind Treatment Period				
System Organ Class/ Preferred Term	PBO <sup>a</sup>  N=136 n (%)	CZP 200mg q2w  N=138 n(%)	CZP 400mg q4w  N=135 n(%)	All CZP <sup>b</sup>  N=332 n(%)
<b>Any AEs in the Cardiac Disorders SOC</b>	1 (0.7)/1	3 (2.2)/3	2 (1.5)/3	5 (1.5)/6
Palpitations	-	1 (0.7)	-	1 (0.3)
Coronary artery disease	-	-	1 (0.7)	1 (0.3)
Acute myocardial infarction	-	1 (0.7)	-	1 (0.3)
Angina unstable	-	-	1 (0.7)	1 (0.3)
Atrial fibrillation	-	-	1 (0.7)	1 (0.3)
Cardiac arrest	-	1 (0.7)	-	1 (0.3)
Tachycardia	1 (0.7)	-	-	-
<b>Any AEs in the Vascular disorders SOC</b>	6 (4.4)/6	8 (5.8)/15	4 (3.0)/4	13 (3.9)/20
Hypertension	5 (3.7)	4 (2.9)	2 (1.5)	7 (2.1)
Hematoma	-	1 (0.7)	-	1 (0.3)
Venous insufficiency	-	1 (0.7)	-	1 (0.3)
Flushing	-	-	1 (0.7)	1 (0.3)
Hot flush	-	1 (0.7)	-	1 (0.3)
Pallor	-	1 (0.7)	-	1 (0.3)
Prehypertension	-	-	1 (0.7)	1 (0.3)
Phlebitis	1 (0.7)	-	-	-
<b>Cardiovascular AEs in General disorders and administration site conditions SOC</b>	1 (0.7)/1	1 (0.7)/1	2 (1.5)/2	3 (0.9)/3
Sudden death	-	-	1 (0.7)/1	1 (0.3)/1
Chest pain	1 (0.7)	1 (0.7)	1 (0.7)	2 (0.6)
<b>Cardiovascular AEs in Nervous system disorders SOC</b>	-	-	1 (0.7)/1	1 (0.3)/1
Cerebrovascular accident	-	-	1 (0.7)	1 (0.3)

a For the entire PBO group, CZP data from PBO subjects were not utilized.

b The All CZP column includes CZP 200mg q2w, CZP 400mg q4w, and escaped PBO subjects with CZP data.

Source: PSA001 Summary of Clinical Safety, Table 2-17, page 101.

Table 45 displays the exposure-adjusted analysis of cardiovascular events through the 24-week Double-Blind Period and through the clinical cutoff date. Like the previous table, the serious cardiovascular events are highlighted; there was an additional 6 cardiovascular events. One of these additional events was fatal and was previously described in Section 7.3.1 Deaths.

Overall, the exposure-adjusted incidence rate of cardiovascular events is low across treatment arms. The incidence rate is numerically higher in the CZP-treated groups as compared to placebo. However, as it has been seen in other safety categories, the incidence rate numerically decreased with increased exposure. The event with the highest incidence rate was hypertension.

**Table 45. Exposure-Adjusted Summary of Cardiovascular Events in PsA001**

System Organ Class/ Preferred Term	Double Blind Safety Pool (0-24 wks)			All CZP Safety Pool (data cut-off 31 May 2012)	
	PBO N = 136	CZP 200mg q2wks N = 169	CZP 400mg q4wks N = 165	CZP 200mg q2wks N=197	CZP 400mg q4wks N=196
Patient exposure years	51.1	66.9	64.6	232.4	226.3
	n/# of events (incidence per 100 patient-years)				
<b>All AEs in Cardiac disorders SOC</b>	<b>1 /1 (1.96)</b>	<b>3/3 (4.53)</b>	<b>2/3 (3.12)</b>	<b>6/7 (2.62)</b>	<b>4/6 (1.80)</b>
Palpitations	-	1/1 (1.50)	-	1/2(0.43)	1/1 (0.44)
Coronary artery disease	-	-	1/1 (1.56)	-	1/1 (0.44)
Angina unstable	-	-	1/1 (1.56)	1/1 (0.43)	1/1 (0.44)
Myocardial infarction	-	-	-	1/1 (0.43)	1/1 (0.44)
Acute myocardial infarction	-	1/1 (1.50)	-	1/1 (0.43)	-
Angina pectoris	-	-	-	-	1/1 (0.44)
Myocarditis	-	-	-	1/1 (0.43)	-
Atrial fibrillation	-	-	1/1 (1.55)	-	1/1 (0.45)
Cardiac arrest	-	1/1 (1.49)	-	1/1 (0.43)	-
Tachycardia	1/1 (1.96)	-	-	-	-
<b>Any AEs in the Vascular disorders SOC</b>	<b>6/6</b>	<b>11/18 (17.19)</b>	<b>4/4 (6.28)</b>	<b>19/29 (8.74)</b>	<b>12/12 (5.57)</b>
Hypertension	5 /5	7/7 (10.75)	2/2 (3.10)	13/14 (5.84)	7/7 (3.17)
Hematoma	-	1/1 (1.50)	-	1/1 (0.43)	-
Lymphedema	-	-	-	1/1 (0.43)	-

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Venous thrombosis	-	-	-	1/1 (0.43)	-
Venous insufficiency	-	1/1 (1.50)	-	1/1 (0.43)	-
Deep vein thrombosis	-	-	-	1/1 (0.43)	-
Flushing	-	-	1/1 (1.56)	-	1/1 (0.45)
Hot flush	-	1/1 (1.50)	-	1/2 (0.43)	1/1 (0.44)
Pallor	-	1/8 (1.50)	-	1/8 (0.43)	-
Prehypertension	-	-	1/1 (1.56)	-	1/1 (0.44)
Phebitis	1/1	-	-	-	2/2 (0.89)
<b>Cardiovascular AEs in General disorders and administration site conditions SOC</b>	<b>1/1 (1.96)</b>	<b>1/1 (1.59)</b>	<b>2/2 (3.57)</b>	<b>3/3 (1.43)</b>	<b>4/4 (0.98)</b>
Sudden death	-	-	1/1 (1.55)	-	1/1 (0.44)
Chest pain	1	1/1 (1.50)	1/1 (1.55)	2/2 (0.87)	2/2 (0.89)
Chest discomfort	-	-	-	1/1 (0.43)	1/1 (0.44)
Cardiovascular AEs in Nervous					
<b>Cardiovascular AE in Nervous system disorders SOC</b>	<b>-</b>	<b>-</b>	<b>1/1 (1.62)</b>	<b>-</b>	<b>2/2 (0.97)</b>
Cerebrovascular accident	-	-	1/1 (1.55)	-	1/1 (0.44)
Transient ischemic attack	-	-	-	-	1/1 (0.44)

Source: PSA001 Summary of Clinical Safety Global Tables, Table 8.11:1, pages 1077-1262.

Based on the above findings, there does not appear to be a new safety signal. The incidence of CV events is similar to what has been seen in RA patients and what has been reported with other anti-TNF $\alpha$  therapies.

### *Demyelinating Disorders*

Demyelinating disorders have been described with other TNF $\alpha$  inhibitors. No cases of demyelinating disorders or neurologic events (other than the cerebrovascular accident and transient ischemic attack that were categorized with CV events) were reported in the 24-week Double Blind Treatment Period or through the clinical cutoff date. Of note, no cases of demyelinating disorders have been described with certolizumab and RA subjects either.

### *Skin Disorders and Autoimmune Disorders*

In the Double-Blind Treatment Period, there was one case of cutaneous lupus erythematosus (CLE) in a 64-year-old female in the CZP 200mg q2w treatment arm (Subject (b) (6)). She developed the skin condition 45 days after starting the study medication. The study medication was not stopped during the Double-Blind period because of this event. Later, as the CLE persisted, the study medication was discontinued during the Dose-Blind Treatment Period. No other skin or autoimmune disorders were reported through the data cutoff date, other than the presence of psoriasis itself. In RA subjects, there have been cases of sarcoidosis and lupus-like illness in CZP-treated subjects. In summary, there are no new safety signals.

### *Injection Site Reactions and Hypersensitivity*

UCB, Inc. describes injection site reactions as local or systemic. Systemic injection site reactions are essentially systemic hypersensitivity reactions, such as facial edema, pruritus, nausea/vomiting. These systemic hypersensitivity reactions were further categorized as acute or delayed. Overall, there were more injection site reactions in the CZP-treated subjects than in the placebo-treated group. The number of local injection site reactions likely contributed to this finding. There were more local injection site reactions in the CZP treated subjects, and the CZP 400mg group outnumbered the CZP 200mg group. On the other hand, the systemic hypersensitivity reactions were generally comparable across all treatment arms. In fact, the only subject to develop an acute systemic hypersensitivity reaction was one who received placebo. Table 46 summarizes these injection site reactions through the Double-Blind Treatment Period.

Thus, there does not appear to be a new safety signal in regards to hypersensitivity reactions.

**Table 46. Summary of Injection-Site Reactions During Double-Blind Treatment Period of PsA001**

<b>Summary of Injection Reactions during Double-Blind Treatment Period</b>				
<b>System Organ Class/ Preferred Term</b>	<b>PBO<sup>a</sup></b>	<b>CZP 200mg q2w</b>	<b>CZP 400mg q4w</b>	<b>All CZP<sup>b</sup></b>
	<b>N=136 n (%)</b>	<b>N=138 n (%)</b>	<b>N=135 n (%)</b>	<b>N=332 n (%)</b>
<b>Any injection reaction TEAE</b>	5 (3.7)	8 (5.8)	16 (11.9)	25 (7.5)
<b>Any local injection site reaction TEAE</b>	3 (2.2)	7 (5.1)	15 (11.1)	22 (6.6)
<b>Any systemic injection reaction TEAE</b>	2 (1.5)	2 (1.4)	2 (1.5)	5 (1.5)
<b>Any acute systemic injection reaction TEAE</b>	1 (0.7)	-	-	-
<b>Any delayed systemic injection reaction TEAE</b>	1 (0.7)	2 (1.4)	2 (1.5)	5 (1.5)

a For the entire PBO group, CZP data from PBO subjects were not utilized.

b The All CZP column includes CZP 200mg q2w, CZP 400mg q4w, and escaped PBO subjects with CZP data.

Source: PSA001 Summary of Clinical Safety, Table 2-23, page 120.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Table 47 displays the most common AEs (by PT) that occurred during the Double-Blind Treatment period. In general, the number of adverse events was similar across treatment groups. The most common events in the CZP-treated subjects were nasopharyngitis, upper respiratory infection, some laboratory abnormalities (increased alanine aminotransferase and increased creatine phosphokinase), and diarrhea. For both doses of CZP, the numbers were generally comparable although nasopharyngitis was greater in the CZP 200mg group (13.0% for CZP 200mg vs. 6.7% for CZP 400mg). For placebo subjects, nasopharyngitis and upper respiratory tract infection were also common AEs although urinary tract infections outnumbered upper respiratory tract infection.

In conclusion, the type and incidence of common adverse events are consistent with those seen in PsA patients treated with systemic immunosuppressive therapies. There is no new safety signal.

**Table 47. Summary of Common AEs (>2%) in the Double-Blind Treatment Period, by PT**

Summary of Common AEs during Double-Blind Treatment Period				
Preferred Term	PBO <sup>a</sup>	CZP 200mg q2w	CZP 400mg q4w	All CZP <sup>b</sup>
	N=136 n (%)	N=138 n(%)	N=135 n(%)	N=332 n(%)
Any AEs n(%)# of events	92 (67.6)/260	94 (68.1)/303	96 (71.1)/305	207 (62.3)/636
Nasopharyngitis	10 (7.4)	18 (13.0)	9 (6.7)	29 (8.7)
Upper respiratory tract infection	7 (5.1)	12 (8.7)	13 (9.6)	26 (7.8)
Alanine aminotransferase increased	2 (1.5)	4 (2.9)	7 (5.2)	12 (3.6)
Diarrhea	4 (2.9)	7 (5.1)	5 (3.7)	12 (3.6)
Blood creatine phosphokinase increased	4 (2.9)	5 (3.6)	6 (4.4)	12 (3.6)
Headache	2 (1.5)	6 (4.3)	5 (3.7)	12 (3.6)
Aspartate aminotransferase increased	1 (0.7)	4 (2.9)	6 (4.4)	10 (3.0)
Pharyngitis	3 (2.2)	6 (4.3)	4 (3.0)	10 (3.0)
Sinusitis	1 (0.7)	3 (2.2)	6 (4.4)	9 (2.7)
Hepatic enzyme increased	2 (1.5)	5 (3.6)	4 (3.0)	9 (2.7)
Bronchitis	6 (4.4)	4 (2.9)	4 (3.0)	8 (2.4)
Abdominal pain upper	2 (1.5)	5 (3.6)	3 (2.2)	8 (2.4)
Fatigue	2 (1.5)	4 (2.9)	4 (3.0)	8 (2.4)
Oral herpes	3 (2.2)	2 (1.4)	4 (3.0)	8 (2.4)
Urinary tract infection	9 (6.6)	3 (2.2)	4 (3.0)	7 (2.1)
Hypertension	5 (3.7)	4 (2.9)	2 (1.5)	7 (2.1)

a For the entire PBO group, CZP data from PBO subjects were not utilized.

b The All CZP column includes CZP 200mg q2w, CZP 400mg q4w, and escaped PBO subjects with CZP data.

Source: PsA001 Summary of Clinical Safety, Table 2\_3, page 52-53.

## 7.4.2 Laboratory Findings

Study PsA001 defined markedly abnormal values as laboratory values of Grade 3 or 4 according to the RCTC. Table 48 summarizes these laboratory criteria.

**Table 48. Definition of Markedly Abnormal Laboratory Values**

Laboratory parameter	Grade 3 or 4 according to the RCTC values
<b>Hematology</b>	
Hemoglobin	< LLN and decrease from Baseline >2g/dL <8g/dL
Platelets	<50000/ $\mu$ L
White blood cells	<2000/ $\mu$ L
Neutrophils	<1000/ $\mu$ L
Lymphocytes	<1000/ $\mu$ L
<b>Serum biochemistry</b>	
Sodium	<125mmol/L
Potassium	>6.4mmol/L <3mmol/L
Total calcium	>12.5mg/dL <7mg/dL
Creatine kinase (CK)	>4x ULN
Glucose	>250mg/dL <40mg/dL
Creatinine	>1.8x ULN
Uric acid	$\geq$ 3x ULN
Alkaline phosphatase	>3x ULN
Aspartate aminotransferase (AST)	>3x ULN
Alanine aminotransferase (ALT)	>3x ULN
Bilirubin	$\geq$ 2x ULN

LLN=lower limit of normal; RCTC= Rheumatology Common Toxicity Criteria; ULN=upper limit of normal  
 Source: Summary of Clinical Safety, Table 1\_3, page 28.

TNF $\alpha$  inhibitors have been associated with elevated liver enzymes and hepatitis. For example, infliximab includes a WARNING stating that “severe hepatic reactions, including acute liver failure ... have been reported rarely in postmarketing data in patients receiving” infliximab. In fact, even certolizumab pegol has a line listing “elevated liver enzymes and hepatitis” in the ADVERSE REACTIONS (postmarketing). Mechanistically, TNF $\alpha$  exerts pleiotropic effects in the liver, as both a mediator of hepatotoxicity and in maintaining functional liver mass by driving hepatocyte proliferation and regeneration (Schwabe 2006). Because of these dual roles, there is no clearly anticipated effect of TNF $\alpha$  inhibition on the liver.

Table 49 lists the number of subjects with elevated liver-associated enzymes during the Double-Blind Treatment Period of PsA001. Cases of elevated liver

enzymes actually were quite similar across treatment arms, particularly in the higher liver enzymes elevation. For the lower enzymes elevations (AST or ALT  $\geq 3xULN$  and Bilirubin  $\geq 1xULN$ ), the CZP-treated subjects had more cases than placebo with a numerically higher proportion in the CZP 400mg group than the CZP 200mg group. According to the *Drug-Induced Liver Injury: Premarketing Clinical Evaluation Guidance*, Hy's Law cases are defined by an ALT or AST  $\geq 3xULN$  and total bilirubin  $\geq 2xULN$ . Based on this definition, there were no Hy's Law cases in PsA001.

**Table 49. Post-Baseline Liver Associated Enzymes Elevations During the Double-Blind Treatment Period of PsA001**

Post-Baseline Liver Associated Enzymes Elevation during Double-Blind Treatment Period					
Parameter	Criteria	PBO <sup>a</sup>  N=136 n (%)	CZP 200mg q2w  N=138 n(%)	CZP 400mg q4w  N=135 n(%)	All CZP <sup>b</sup>  N=332 n(%)
AST	$\geq 3xULN$	1 (0.7)	2 (1.4)	3 (2.2)	5 (1.5)
	$\geq 5xULN$	-	-	-	-
	$\geq 10xULN$	-	-	-	-
	$\geq 20xULN$	-	-	-	-
ALT	$\geq 3xULN$	3 (2.2)	5 (3.6)	7 (5.2)	12 (3.6)
	$\geq 5xULN$	2 (1.5)	2 (1.4)	2 (1.5)	4 (1.2)
	$\geq 10xULN$	-	-	-	-
	$\geq 20xULN$	-	-	-	-
AST or ALT	$\geq 3xULN$	3 (2.2)	5 (3.6)	7 (5.2)	12 (3.6)
	$\geq 5xULN$	2 (1.5)	2 (1.4)	2 (1.5)	4 (1.2)
	$\geq 10xULN$	-	-	-	-
	$\geq 20xULN$	-	-	-	-
Bilirubin	$\geq 1xULN$	4 (2.9)	4 (2.9)	9 (6.7)	16 (4.8)
	$\geq 1.5xULN$	-	-	4 (3.0)	5 (1.5)
Alkaline Phosphatase	$\geq 1.5xULN$	-	1 (0.7)	1 (0.7)	2 (0.6)
Bilirubin AND ALT or AST	$\geq 1xULN$ $\geq 3xULN$	-	-	3 (2.2)	3 (0.9)

a For the entire PBO group, CZP data from PBO subjects were not utilized.

b The All CZP column includes CZP 200mg q2w, CZP 400mg q4w, and escaped PBO subjects with CZP data.

Source: PSA001 Summary of Clinical Safety, Table 2-21, page 116 and Table 2-22, page 118.

Table 50 the exposure-adjusted summary of cases of clinical hepatotoxicity events. During the Double-Blind Treatment Period, the exposure-adjusted incidence rate is higher in the CZP-treated subjects than in placebo. However, with longer exposure, the incidence rate declines. The incidence is also very comparable in the two doses of CZP. The most common clinical event is elevations in the liver associated enzymes. Other than hepatic steatosis, most of the PTs are single events.

**Table 50. Exposure-Adjusted Summary of Hepatic AEs in PsA001**

High Level Term/ Preferred Term	Double Blind Safety Pool (0-24 wks)			All CZP Safety Pool (data cut-off 31 May 2012)	
	PBO N = 136	CZP 200mg q2wks N = 169	CZP 400mg q4wks N = 165	CZP 200mg q2wks N=197	CZP 400mg q4wks N=196
Patient exposure years	51.1	66.9	64.6	232.4	226.3
n/# of events (incidence per 100 patient-years)					
Any hepatic AEs	8/13 (15.6)	14/17 (22.03)	13/25 (21.71)	28/45 (13.29)	21/43 (10.24)
Cholestasis and jaundice	1/1	-	-	-	1/1 (0.44)
Hyperbilirubinemia	-	-	-	-	1/1 (0.44)
Jaundice	1/1	-	-	-	-
Hepatic and Hepatobiliary disorders NEC	-	1/1(1.50)	1/1 (155)	1/1 (0.43)	1/1 (0.44)
Liver disorder	-	1/1(1.50)	1/1 (1.55)	1/1 (0.43)	1/1 (0.44)
Heptic enzymes and function abnormalities	1/1	-	1/1 (1.56)	1/1 (0.43)	1/1 (0.44)
Hypertransaminasemia	1/1	-	1/1 (1.56)	1/1 (0.43)	1/1 (0.44)
Hepatobiliary signs and symptoms	-	1/1 (1.50)	-	1/1 (0.43)	-
Hepatic pain	-	1/1 (1.5)	-	1/1 (0.43)	-
Hepatocellular damage and hepatitis NEC	1/1	-	-	2/2 (0.87)	-
Hepatic steatosis	1/1	-	-	2/2 (0.87)	-
Liver function analyses	5/10	12/15 (18.66)	12/23 (19.94)	24/40 (11.19)	19/39 (9.16)
Alanine aminotransferase increased	2/3	4/4 (6.05)	6/8 (9.61)	9/11 (4.00)	10/12 (4.63)
Aspartate aminotransferase increased	1/1	3/3 (4.53)	5/5 (7.94)	4/7 (1.75)	9/10 (4.14)
Hepatic enzyme increased	2/3	5/5 (7.60)	4/5 (6.32)	8/9 (3.53)	5/6 (2.26)
Gamm-glutamyltransferase increased	1/2	1/1 (1.50)	2/2 (3.12)	3/5 (1.31)	5/6 (2.25)
Liver function test abnormal	1/1	1/1 (1.50)	2/2 (3.14)	4/5 (1.74)	2/2 (0.89)
Blood bilirubin increased	-	-	1/1 (1.56)	1/2 (0.43)	1/1 (0.44)
Transaminases increased	-	1/1 (1.50)	-	1/1 (0.43)	1/2 (0.44)
Tissue enzymes analyses NEC	-	-	-	-	1/1 (0.44)
Blood alkaline phosphatase increased	-	-	-	-	1/1 (0.44)

Source: Summary of Clinical Safety, Table 2-18, pages 107-108.  
 Summary of Clinical Safety Tables, Table 8.11:5, pages 1367-1374  
 PSA001 Tables, Table 8.2.1

Like hepatotoxicity, most of the approved TNF $\alpha$  inhibitors (to include certolizumab pegol) have WARNINGS regarding hematological cytopenias including pancytopenia, aplastic anemia, leucopenia, and thrombocytopenia. In PsA001, the markedly abnormal laboratory values were small. Table 51 summarizes the findings in the Double-Blind Treatment Period. The most common hematologic laboratory abnormality was markedly abnormal low lymphocytes in both the placebo and CZP arms. In fact, the cases of lymphopenia were actually higher than the CZP groups. With longer exposure (through the data cutoff date), the proportion of cases of lymphopenia stayed consistent. The next most common event was neutropenia. All hematologic events were mild and nonserious.

**Table 51. Summary of Abnormal Post-baseline Hematology Values During the Double-Blind Treatment Period**

Summary of Abnormal Post-baseline Hematology Values During Double-Blind Treatment Period					
Parameter	Criteria	PBO <sup>a</sup>  N=136 n (%)	CZP 200mg q2w  N=138 n(%)	CZP 400mg q4w  N=135 n(%)	All CZP <sup>b</sup>  N=332 n(%)
Overall	At least 1 MA high TE value	-	-	-	-
	At least 1 MA low TE value	18 (13.2)	9 (6.5)	9 (6.7)	24 (7.2)
Hemoglobin	At least 1 MA high TE value	-	-	-	-
	At least 1 MA low TE value	1 (0.7)	-	-	1 (0.3)
Platelets	At least 1 MA high TE value	-	-	-	-
	At least 1 MA low TE value	-	1 (0.7)	-	1 (0.3)
Neutrophils	At least 1 MA high TE value	-	-	-	-
	At least 1 MA low TE value	-	2 (1.4)	1 (0.7)	4 (1.2)
Lymphocytes	At least 1 MA high TE value	-	-	-	-
	At least 1 MA low TE value	17 (12.5)	6 (4.3)	9 (6.7)	20 (6.0)

a For the entire PBO group, CZP data from PBO subjects were not utilized.

b The All CZP column includes CZP 200mg q2w, CZP 400mg q4w, and escaped PBO subjects with CZP data.

Source: PSA001 Summary of Clinical Safety, Table 3-26, page 128.

Table 52 summarizes the markedly abnormal chemistry values in PsA001. The proportion of subjects with abnormal chemistry values is low. The CZP-treated subjects have more abnormal chemistry values than the placebo subjects. The most common abnormal chemistry value was elevated ALT, as already discussed above. The next most common abnormal chemistry value was elevated creatine kinase and elevated glucose. These two laboratory values – creatine kinase and elevated glucose – were generally equal across treatment arms. Most of the proportions of abnormal values stay relatively the same with increased exposure through the clinical cutoff date.

**Table 52. Summary of Abnormal Post-baseline Chemistry Values During the Double-Blind Treatment Period**

Summary of Abnormal Post-baseline Chemistry Values During Double-Blind Treatment Period					
Parameter	Criteria	PBO <sup>a</sup>  N=136 n (%)	CZP 200mg q2w  N=138 n(%)	CZP 400mg q4w  N=135 n(%)	All CZP <sup>b</sup>  N=332 n(%)
<b>Overall</b>	At least 1 MA high TE value	8 (5.9)	14 (10.1)	16 (11.9)	32 (9.6)
	At least 1 MA low TE value	-	-	1 (0.7)	1 (0.3)
<b>Potassium</b>	At least 1 MA high TE value	-	-	1 (0.7)	1 (0.3)
	At least 1 MA low TE value	-	-	1 (0.7)	1 (0.3)
<b>Creatine Kinase</b>	At least 1 MA high TE value	3 (2.2)	6 (4.3)	3 (2.2)	9 (2.7)
	At least 1 MA low TE value	-	-	-	-
<b>Glucose</b>	At least 1 MA high TE value	2 (1.5)	3 (2.2)	5 (3.7)	9 (2.7)
	At least 1 MA low TE value	-	-	-	-
<b>AST</b>	At least 1 MA high TE value	1 (0.7)	2 (1.4)	3 (2.2)	5 (1.5)
	At least 1 MA low TE value	-	-	-	-
<b>ALT</b>	At least 1 MA high TE value	3 (2.2)	5 (3.6)	7 (5.2)	12 (3.6)
	At least 1 MA low TE value	-	-	-	-
<b>Bilirubin</b>	At least 1 MA high TE value	-	-	-	1 (0.3)
	At least 1 MA low TE value	-	-	-	-

a For the entire PBO group, CZP data from PBO subjects were not utilized.

b The All CZP column includes CZP 200mg q2w, CZP 400mg q4w, and escaped PBO subjects with CZP data.  
 Source: PSA001 Summary of Clinical Safety, Table 3-2, page 132.

In summary, based on the numbers of elevated liver-associated enzymes, markedly abnormal hematology values, and markedly abnormal chemistry values, there does not appear to be a new safety signal.

### 7.4.3 Vital Signs

Heart rate, blood pressure, and respiratory rate were monitored at clinical visits. No significant abnormalities were reported across treatment groups.

### 7.4.4 Electrocardiograms (ECGs)

Routine ECG monitoring was performed periodically. No significant ECG abnormalities were reported except for what was associated with the cardiovascular events already discussed in Section 7.3.5 Submission Specific Primary Safety Concerns.

### 7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted with this supplement.

#### 7.4.6 Immunogenicity

A “positive” finding of anti-CZP antibody was based on the assay results of >2.4 units/mL. If a subject was “positive” at any time during the 24-week Double-Blind period, he/she was considered “positive.” In PsA001, 10.8% of subjects who were exposed to CZP had a “positive” anti-CZP antibody status. The proportion of subjects with positive anti-CZP antibodies was nearly equivalent for each dose of CZP. The first positive test occurred most frequently around Week 12.

Table 53 shows a summary of adverse events by anti-CZP antibody positivity and specifically after developing positive antibody status. There does appear to be a slightly higher number of AE in subjects with positive antibody status, and most of these AEs did occur after the subjects tested positive for anti-CZP antibodies.

**Table 53. Summary of AEs by Anti-CZP Antibody Status During the Double-Blind Treatment Period (Wks 0-24)**

	Anti-CZP antibody status			
	Any CZP exposure	Negative	Positive	After the onset of positive Ab status
	N=332 n (%)	N=296 n (%)	N=36 n (%)	N=36 n (%)
<b>Any TEAEs</b>	207 (62.3)	180 (60.8)	27 (75.0)	15 (41.7)
<b>Severe TEAEs</b>	15 (4.5)	13 (4.4)	2 (5.6)	1 (2.8)
<b>Drug-related TEAEs</b>	86 (25.9)	74 (25.0)	12 (33.3)	7 (19.4)
<b>Serious TEAEs</b>	22 (6.6)	19 (6.1)	4 (11.1)	3 (8.3)
<b>Discontinuations due to TEAEs</b>	10 (3.0)	9 (3.0)	1 (2.8)	1 (2.8)
<b>Death</b>	2 (0.6)	2 (0.7)	-	-

Source: PSA001 Summary of Clinical Safety, Table 2-24, page 124.

A correlation of efficacy to anti-CZP antibody is discussed in Section 6.1.7.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

PsA001 provided controlled data to allow exploration of dose-dependency and comparison between subjects treated with placebo, CZP 200mg q2w, and CZP 400mg q4w. Exposure-adjusted incidence rates of major safety parameters indicate no clear dose-dependent increase with the two doses. This was particularly true with longer exposure, and this might be expected given that these are essentially the same cumulative dose.

### 7.5.2 Time Dependency for Adverse Events

The overall exposure-adjusted rates of the various safety parameters appear to be stable with prolonged CZP exposure. In fact, the incidence rates seemed to decrease with longer exposure. However, this finding should be interpreted critically, as the longer exposure data comes from the uncontrolled portion of the study.

### 7.5.3 Drug-Demographic Interactions

Adverse events were analyzed by gender. Through the clinical data cutoff date, there was little overall difference in the number of AEs between males and females. However, there were more females who discontinued study drug because of an AE.

Of note, in the RA studies, there were no major differences in AEs reviewed for a variety of demographic characteristics (gender, age, race, baseline MTX use, baseline steroid use, previous TNF $\alpha$  inhibitor therapy). In conclusion, no new signals were noted in drug-demographic interactions in study PsA001.

### 7.5.4 Drug-Disease Interactions

No specific drug-disease interactions have been noted in the CZP development program in PsA and other indications.

### 7.5.5 Drug-Drug Interactions

Because DMARDs (particularly, MTX) can be associated with hepatotoxicity, there was an evaluation of effect of concomitant DMARD use on clinical hepatotoxic events. Table 54 gives a brief overview on the number of clinical hepatotoxic events based on

DMARD use during the 24-week Double-Blind Treatment Period. There does appear to be a greater difference between CZP-treated groups and placebo in the number of hepatotoxic events. There were more hepatotoxic events in subjects who received CZP and concomitant DMARDs compared to placebo who only received DMARDs. For the subjects who did not receive concomitant DMARDs, the number of hepatotoxic events was quite similar across treatment arms. However, overall, the proportion of subjects who had a hepatotoxic clinical event was low and was quite similar across the same treatment arm – e.g., the number of All CZP subjects who had a hepatotoxic event was very comparable whether subjects were taking DMARDs.

**Table 54. Hepatic AEs by Baseline DMARD Use During the Double-Blind Treatment Period**

	PBO	CZP 200mg q2w	CZP 400mg q4w	CZP 200mg q2w + CZP 400mg q4w
	N=136 n (%)	N=168 n (%)	N=164 n (%)	N=332 n (%)
<b>Baseline DMARD use, N</b>	86	111	113	224
<b>Any hepatic AEs</b>	4 (4.7)	8 (7.2)	11 (9.7)	19 (8.5)
<b>No Baseline DMARD use, N</b>	50	57	51	108
<b>Any hepatic AEs</b>	4 (8.0)	7 (12.3)	4 (7.8)	11 (10.2)

Source: Summary of Clinical Safety, Table 2\_19, pages 109-110.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

Data on malignancies and neoplasm was reviewed in 7.3.5 Submission Specific Primary Safety Concerns.

### 7.6.2 Human Reproduction and Pregnancy Data

In PsA001, during the Double-Blind Treatment Period, there was 1 pregnancy and 1 pregnancy of a partner.

- Subject (b) (6), 35-year-old female was randomized to the CZP 400mg q4w treatment arm. She had a positive pregnancy test after 142 days in the study. The study drug was permanently discontinued. Of note, the subject had a full-term pregnancy and delivered vaginally. At 1 month after birth, her child appeared to be healthy. The subject, however, had exacerbation of her psoriasis but stability in her arthritis.

- Subject [REDACTED] <sup>(b) (6)</sup>, 27-year-old male was randomized to the CZP 400mg q4w treatment arm. His partner had a reported positive pregnancy test 101 days after study treatment. The subject's partner had an abortion at 10 weeks of pregnancy, but no other information is known about this pregnancy.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

No specific information on pediatrics and assessment on growth were provided in this submission.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdue, abuse, and dependence potential of CZP have not been specifically evaluated. In the PsA development program, the highest known doses were those recommended, 200mg sc and 400mg sc. In the RA development program, the highest known doses were 20mg/kg iv and 800mg sc.

Withdrawal also has not been evaluated in the PsA clinical development program. One of the RA studies (C87076) utilized a withdrawal design, but only 24 subjects were part of the withdrawal phase. No safety signals were identified. Per UCB, Inc., the other trials did not have a withdrawal phase, but 119 subjects were off CZP for approximately 42 days. No specific analysis of safety events was performed on these subjects.

## 7.7 Additional Submissions / Safety Issues

Information from additional submissions has been incorporated into the applicable safety sections of this review.

The 120-day safety report (submitted in March 2013) did not reflect any significant new safety signals. Overall, the pattern and incidence of SAEs were similar to what was seen in the original filing. There were no additional deaths. There was one additional malignancy (thyroid cancer). No new cases of anaphylaxis or serious injection reactions were reported.

## 8 Postmarket Experience

Certolizumab pegol was first approved in Switzerland on 7 September 2007 for the treatment of severe active Crohn's Disease. It was approved in the United States for Crohn's Disease in April 2008 and, subsequently, for RA in May 2009. As of May 2012, Cimzia is approved in 38 countries and is marketed in 30 countries around the world.

A Postmarketing Surveillance Report (PMSR) was submitted that summarized events from 7 September 2007 to 31 May 2012. The report describes mostly cases from the currently approved indications of Crohn's Disease and Rheumatoid Arthritis. The total number of serious adverse drug reaction (ADR) cases was 3068. One hundred twenty-two of these cases led to death (approximately 4%). Most of the cases are those that are labeled in the US Package Insert (USPI) and are what is expected with other TNF $\alpha$  inhibitors.

Two types of rare malignancies – hepatosplenic T-cell lymphoma (HSTCL) and merkel cell carcinoma of the skin – were described in subjects taking certolizumab pegol. Because of the case of HSTCL, the FDA did issue a safety alert in April 2011 regarding HSTCL in young adult male patients with Crohn's Disease who were treated with TNF $\alpha$  blockers and concomitant or prior immunomodulators.

Based on the PMSR, no new safety signals have been identified.

## 9 Appendices

### 9.1 Literature Review/References

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3. Cassell SE, et al. "The modified nail psoriasis severity index: validation of an instrument to assess psoriatic nail involvement in patients with psoriatic arthritis." *J Rheumatol.* 2007;34:123-9.
4. Dixon WG, et al. "Serious infection following anti-Tumor Necrosis Factor $\alpha$  therapy in patients with rheumatoid arthritis." *Arthritis Rheum.* 2007;56:2896-2904.

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM354468.pdf>
6. Dworkin RH, et al. "Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations." *J Pain*. 2008;9:105-21.
7. Healy PJ and Helliwell PS. "Measuring dactylitis in clinical trials: which is the best instrument to use?" *J Rheumatol*. 2007;34:1302-6.
8. Mease PJ, et al. "Psoriatic arthritis assessment tools in clinical trials." *Ann Rheum Dis*. 2005; 64 (Suppl II):ii49-ii54
9. Schwabe R and Brenner D. "Mechanisms of liver injury: TNF- $\alpha$ -induced liver injury: role of IKK, JNK, and ROS pathways." *Am J Physiol Gastrointest Liver Physiol*. 2006;290:G583-589.
10. Strand V, et al. "Physical function and health related quality of life: analysis of 2-year data from randomized, controlled studies of leflunomide, sulfasalazine, or methotrexate in patients with active rheumatoid arthritis." *J Rheumatol*. 2005;32:590-601.
11. Van der Heijde D, et al. "Psoriatic arthritis imaging: a review of scoring methods." *Ann Rheum Dis*. 2005;64:ii61-ii64.

## 9.2 Labeling Recommendations

The following are the major revisions recommended for UCB's proposed labeling for certolizumab pegol for psoriatic arthritis. These recommendations may change after internal labeling discussions and after labeling discussions with (b) (4)

### DOSAGE and ADMINISTRATION

1. UCB's proposed dosing for PsA is not supported for the data. For all of the primary and key secondary endpoints, the treatment effect is lower in subjects who received certolizumab pegol 400mg q4w. See full discussion in Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.

The Division's recommended dosing is the following (consistent with approved RA dosing): 400mg initially and at Weeks 2 and 4, followed by 200mg every other week; for maintenance dosing, 400mg every 4 weeks can be considered.

## CLINICAL STUDIES

2. Based on the prespecified hierarchal analysis plan, (b) (4)  
(b) (4) Instead, it can be referred to as an efficacy variable.  
In fact, the line should just be reworded.
3. (b) (4)  
(b) (4) This line should be removed.
4. The sentence about (b) (4) use should be reworded.
5. All references to the (b) (4) should be deleted. (b) (4)  
(b) (4)  
(b) (4) confirmed that the inclusion of (b) (4) on the label is not recommended.
6. In Table 8, ACR 20 components at Week 12 (primary endpoint) may be included.  
(b) (4) should be deleted.
7. As already noted, references to (b) (4) should be removed in Table 8 (b) (4)  
Table 8 (b) (4) should also be removed (per statistical team).
8. The radiographic response will be reworded by the Statistical Team to reflect the re-analysis of the radiographic data.
9. The HAQ-DI section will be revised to take out (b) (4) As this was not a (b) (4) (b) (4) are not relevant.
10. (b) (4) are patient-reported outcomes (PROs) (b) (4)  
(b) (4) In addition, (b) (4) should be deleted.

### 9.3 Advisory Committee Meeting

No new Advisory Committee (AC) meeting was deemed necessary for this submission, as no issue issues were identified during the review process to warrant AC discussion.



**Table 32. Schedule of Assessments for Study PSA001 (cont)**

Protocol activity	Scr -5 to -1	BL 0	Weeks																								Every 4 * weeks H	Every 4** weeks	Every 12** weeks	158 or W/D	SFU ***	
			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
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	
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	
Productivity <sup>10</sup>		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 <sup>11</sup>		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	
CZP plasma concentration/ anti-CZP Abs		X	X	X	X			X	X			X													X				X <sup>a</sup>	X	X	
LEI		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	
LDI		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	
mNAPSI <sup>15</sup>		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	
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
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
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
Study drug sc <sup>12</sup>		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		

Abs=antibodies; AEs=adverse events; BASDAI=Bath Ankylosing Spondylitis Disease Index; BL=Baseline; BSA=body surface area; CRP=C-reactive protein; CZP=certolizumab pegol; DLQI=Dermatology Life Quality Index; PGAP=Physician’s Global Assessment of Psoriasis; EQ-5D=EuroQoL Health Status Questionnaire; H=home, no site visit; Inv=Investigator; IVRS=Interactive Voice Repsonse System; LDI=Leeds Dactylitis Index; LEI=Leeds Enthesitis Index; mNAPSI=modified Nail Psoriasis Severity Index; PASI=Psoriasis Arthritis Severity Index; PPD=purified protein derivative; PE=physical exam; PsA=psoriatic arthritis; PsAQoL=Psoriatic Arthritis Quality of Life; sc=subcutaneously; Scr=Screening; SF-36=Short-Form 36-item Health Survey; SFU=Safety Follow-Up; TB=tuberculosis; W/D=Withdrawal

1. Weight is to be measured at Screening, Baseline, Weeks 12, 16, 24, 48, 96, and at Completion at Week 158/Withdrawal. Height will be measured at the Baseline Visit only.
2. ESR and testing to rule out hepatitis B surface antigen and antibodies to hepatitis C at Screening only.
3. Pregnancy testing will be serum testing at Screening and urine testing at other visits.
4. Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB.
5. Screening chest x-ray must have occurred within 3 months prior to the Screening Visit and repeated at Weeks 48, 96, and 158.
6. 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.
7. HAQ-DI; Patient’s Assessment of Arthritis Pain (VAS); PGADA (VAS).

Source: Protocol Study PsA001 Amendment 3, Section 5.2, pages 27-29.



## 9.5 Assessment of Efficacy Variables

Appendix 9.5 provides detailed definitions of the efficacy outcomes measured in PsA001.

Several efficacy variables are not discussed in this review, (b) (4) are not on the endpoint hierarchy. Thus, they will not be further defined here. These variables include the following:

- Physician’s Global Assessment of Psoriasis (PGAP)
- Work Productivity Survey (WPS)
- Psoriatic Arthritis Quality of Life (PsAQOL)
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Psoriatic Arthritis Response Criteria (PsARC)
- Disease Activity Score (DAS28)
- Dermatology Life Quality Index (DLQI)
- Modified Nail Psoriasis Severity Index Score (mNAPSI)

### 9.5.1 ACR Responses (ACR 20, ACR 50, ACR 70)

Table 56 defines the ACR responses.

**Table 56. ACR Response**

<b>ACR 20</b>	≥20% improvement in swollen joint count (66 joints) and tender joint counts (68 joints)
	<b>AND</b> ≥20% improvement in 3 of the following 5 components <ul style="list-style-type: none"> <li>• Patient’s assessment of pain by Visual Analog Scale (VAS)</li> <li>• Patient’s global assessment of disease activity by VAS</li> <li>• Physician’s global assessment of disease activity by VAS</li> <li>• Patient’s assessment of physical function as measured by the HAQ-DI</li> <li>• CRP</li> </ul>
<b>ACR 50</b>	Similar definition to ACR 20 except ≥50% improvement
<b>ACR 70</b>	Similar definition to ACR 20 except ≥70% improvement

### 9.5.2 Modified total Sharp score

Radiographs of the hands and feet will be scored with the mTSS, which is defined in Table 57. In Study PSA001, radiographs of the hands and feet (a single posteroanterior

view of each hand and a single dorsoplantar view of each foot) will be taken according to a standardized imaging methodology defined in the “Hand and Foot Radiology Manual,” which is part of the Study Manual. All enrolled subjects will need to have radiographs at baseline, Weeks 12, 24, 48, 96, and completion (Week 158 or Withdrawal). Radiographs will be read centrally and independently by at least 2 experienced readers. The mean score of the readers will be used for analysis. Readers will be blind to treatment assignment and time course of the films.

The efficacy variables include change from baseline in the mTSS as well as the change from baseline in the subcomponents of the mTSS.

**Table 57. Modified Total Sharp-Van der Heijde Score**

<b>Joint Erosion Score</b>	<ul style="list-style-type: none"> <li>• 40 joints of the hand (including DIPs) +12 joints of the feet</li> <li>• Each hand joint: 0-5 (depending on surface area involved) 0 – no erosion 5 – extensive loss of bone from &gt;½ of articulating bone</li> <li>• Each foot joint: 0-10</li> <li>• Maximal erosion score is 320</li> </ul>
<b>Joint Space Narrowing (JSN)</b>	<ul style="list-style-type: none"> <li>• 40 joints of the hand + 12 joints of the feet</li> <li>• Score 0-4 0 – no joint space narrowing 4 – complete joint space loss, bony ankylosis, complete subluxation</li> <li>- Maximal JSN score is 208</li> </ul>

### 9.5.3 Swollen and tender joint counts (66/68 joint evaluations)

- Upper body (6) – bilateral temporomandibular, sternoclavicular, acromioclavicular joints
- Upper extremity (34) – bilateral shoulders, elbows, wrists (including radiocarpal, carpal, and carpometacarpal bones considered as a single unit), metacarpals (MCPs I-V), thumb interphalangeal joints (IP), proximal interphalangeal joints (PIPs II-V), and distal interphalangeal joints (DIPs II-V)
- Lower extremity (28) – bilateral hips, knees, ankles, tarsi (including subtalar, transverse tarsal, and tarsometatarsal as a single unit), metatarsophalangeal joints (MTPs, I-V), great toe IP joints, and PIP joints (II-V)

All sixty-eight joints are evaluated for tenderness, and sixty-six joints (all from above excluding bilateral hips) are evaluated for swelling. Artificial and ankylosed joints are excluded from assessment. Assessed joints are given a grade for swelling and tenderness with 0 being no swelling or tenderness and 1 being detectable synovial thickening or tenderness present, respectively.

In study PSA001, the Principal Investigator, a delegated physician, or a qualified medical professional performed these assessments. Ideally, the same assessor evaluated the subject at each arthritis assessment.

#### 9.5.4 Health Assessment Questionnaire-Disability Index (HAQ-DI) score

Table 58 describes the HAQ-DI.

**Table 58. HAQ-DI score**

<b>20 questions</b>	Score 0 (no difficulty) to 3 (inability to perform task)
<b>8 functional areas</b>	<ul style="list-style-type: none"> <li>- Dressing</li> <li>- Arising</li> <li>- Eating</li> <li>- Walking</li> <li>• Hygiene</li> <li>• Reaching</li> <li>• Gripping</li> <li>• Activities of daily living</li> </ul>
<b>Calculation</b>	<ul style="list-style-type: none"> <li>- Any individual score &lt;2 is adjusted to 2 if the activity requires assistance from another individual or an assistive device</li> <li>- Highest score in each category is summed (0-24) and divided by # of categories scores → total score from 0 to 3</li> </ul>
<b>Minimal clinically important difference (MCID)<sup>1</sup></b>	Decrease in score by 0.30

<sup>1</sup> Meese et al, 2005.

#### 9.5.5 SF-36

The SF-36 is a 36-item generic health-related quality of life (HRQoL) instrument that covers a recall period of 4 weeks. Table 59 presents a description of the SF-36.

**Table 59. Short Form 36 (SF-36)**

<b>8 multi-item scales</b>	<ul style="list-style-type: none"> <li>• Limitations in physical functioning due to health problems (<i>10 items</i>)</li> <li>• Limitations in usual role activities due to physical health problems (<i>4 items</i>)</li> <li>• Bodily pain (<i>2 items</i>)</li> <li>• General mental health (psychological distress and well-being) (<i>5 items</i>)</li> <li>• Limitations in usual role activities due to personal or emotional problems (<i>3 items</i>)</li> <li>• Limitations in social functioning due to physical or mental health problems (<i>2 items</i>)</li> <li>• Vitality (energy and fatigue) (<i>4 items</i>)</li> <li>• General health perception (<i>5 items</i>)</li> <li>• Perceived stability or change in health in the last year (<i>1 item</i>)</li> </ul>
<b>Scale</b>	0 to 100 Higher score indicates better health
<ul style="list-style-type: none"> <li>• <b>Physical Component Summary (PCS)</b></li> <li>• <b>Mental Component Summary (MCS)</b></li> </ul>	Higher score indicates better health Mean of 50 with SD of 10 Compared to general US population norms
<b>MCID<sup>1</sup></b>	SF-36 domains – 5 points SF-36 components – 2.5 points

<sup>1</sup> Strand et al., 2005.

### 9.5.6 Patient’s Global Assessment of Arthritis Pain (VAS)

The pain VAS consists of a horizontal line (100mm in length) on which subjects indicate the level of their arthritis pain at the day of the visit. The question associated with the horizontal line is the following: “Please mark a vertical line on the scale below to show how much pain you have from your arthritis today.” The subject can mark anywhere between 0 (no pain) and 100 (most severe pain). The minimal clinically important difference (MCID) is a change of 10mm (Dworkin et al., 2008).

### 9.5.7 Physician’s Global Assessment of Disease Activity (VAS/Likert Scale)

The Physician’s Global Assessment of Disease Activity (PhGADA) involves the Investigator assessing the overall status of the subject with respect to their PsA signs and symptoms and functional capacity (considering both joint and skin components). The Investigator uses a VAS where 0 is “very good, asymptomatic, and no limitation of normal activity” and 100 is “very poor, very severe symptoms which are intolerable and inability to carry out all normal activities.”

In addition to the VAS, the Investigator utilizes the Likert scale (only for the PsARC assessment) where the subject’s disease signs, functional capacity, and physical

examination are scored on a 5-point scale where 1 is “very good, asymptomatic, and no limitation on normal activity” and 5 is “very poor, very severe symptoms which are intolerable and inability to carry out all normal activities.”

The Investigator will be blind to the subject’s PGADA (described below).

#### 9.5.8 Patient’s Global Assessment of Disease Activity (VAS/Likert Scale)

The Patient’s Global Assessment of Disease Activity (PtGADA) is essentially the same as the PhGADA, except from the subject’s point of view.

For the VAS, the question is “Considering all the ways your arthritis affects you, please mark a vertical line on the scale below to show how you are feeling today.” The subject can respond by marking anywhere between 0 (“very good, no symptoms”) and 100 (“very poor, severe symptoms.” Subjects should consider both joint and skin components in their response to this question.

The Likert scale is essentially the same as that for the PhGADA. The scale is used only for the PsARC measurement and answers the question, “Considering all the ways your arthritis affects you, how are you feeling today?” The scale is the same as that for the PhGADA Likert scale.

#### 9.5.9 Fatigue Assessment Scale (FAS)

The Fatigue Assessment Scale is a validated numeric rating scale with numbers 0 through 10 on a horizontal line. The “0” represents “no fatigue,” and the “10” represents “fatigue as bad as you can imagine.” Subjects rank their fatigue (weariness, tiredness) during the past week. The MCID is 1 point (Belza 1990).

#### 9.5.10 Psoriasis Area and Severity Index Response (PASI)

The PASI is the current gold standard for assessment of extensive psoriasis. The PASI is a measure of the average redness, thickness, and scaliness of the psoriatic lesions (each graded on a 0 to 4 scale), weighted by the area of involvement (body divided into 4 areas – head, upper extremities, trunk, lower extremities). Table 60 defines the PASI responses.

**Table 60. Psoriasis Area and Severity Index Response (PASI)**

<b>PASI score</b>	<ul style="list-style-type: none"><li>• Numeric score 0 to 72</li><li>• Assessing and grading the severity of psoriatic lesions and response to therapy</li></ul>
<b>PASI 50</b>	≥ 50% improvement in PASI score from baseline
<b>PASI 75</b>	≥ 75% improvement in PASI score from baseline
<b>PASI 90</b>	≥ 90% improvement in PASI score from baseline
<b>PASI100</b>	100% improvement in PASI score from baseline

#### 9.5.11 Dactylitis measure (Leeds Dactylitis Index)

The Leeds Dactylitis Index (LDI) is a measure to assess the presence of dactylitis, and the LDI basic is a simplified version of the LDI (Healy and Helliwell, 2007). The LDI measures the ratio of the circumference of the affected digit to the circumference of the same digit on the opposite hand or foot. A “dactylitic digit” is one that has at least ≥10% difference in the circumference of the digit compared to the opposite digit. If both sides are involved, then a table of normative values is used to create the ratio of circumferences. With the LDI basic, the ratio of circumferences is then multiplied by the tenderness score (which is simply 0=absent or 1=present).

#### 9.5.12 Enthesitis measure (Leeds Enthesitis Index)

The Leeds Enthesitis Index (LEI) is a new enthesitis index and was recently adopted for use in randomized controlled trials for PsA. Enthesitis will be assessed by palpation on the lateral epicondyles of the humerus (elbows), medial femoral condyles (knees), and Achilles tendons (heels) and scored as 0 (no pain) or 1 (painful).

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/s/  
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SUZETTE W PENG  
08/26/2013

SARAH K YIM  
08/26/2013



Memorandum

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Division of Pulmonary, Allergy, and  
Rheumatology Products, HFD-570  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

Date: January 17, 2013  
From: Sarah Yim, M.D.  
Associate Director  
To: sBLA 125160/213  
Subject: Filing Review

**I. Introduction**

This is the filing review for supplemental Biologic License Application (sBLA) 125160, supplement 213, for Cimzia (certolizumab pegol) in Psoriatic Arthritis (PsA). Certolizumab is a pegylated anti-TNF $\alpha$  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. Certolizumab is available in a single-use vial (lyophilized powder for reconstitution, 200 mg) and prefilled syringe (PFS) of 200 mg/1 mL. A Risk Evaluation and Mitigation Strategy (REMS) was required to address the risks of serious infection (including tuberculosis and hepatitis B reactivation) and malignancy, as well as heart failure, neurologic reactions, hypersensitivity, cytopenias, and autoimmunity/lupus-like syndromes.

The sponsor's proposed indication is "treatment of adult patients with active psoriatic arthritis."

**II. Background/Regulatory History in PsA**

IND 9869 was originally opened on June 8, 2001 for the Crohn's disease indication. In September 2005, with the reassignment of products from the CBER Division of Therapeutic Biologic Medicine Products to the CDER review divisions, the Crohn's disease protocols were

consolidated under IND 11197, overseen by the Division of Gastroenterology Products (DGP) and the rheumatic disease protocols remained under IND 9869, overseen by the then Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP). The applicant submitted an End-of-Phase 2 (EOP2) meeting request for the PsA and Axial Spondyloarthritis (AxSpA) indications in March 2009. This meeting request was denied but written responses were provided to the sponsor after consultation was obtained from the Study Endpoints and Labeling Development (SEALD) team regarding the proposed use of patient-reported outcome (PROs) measures in the proposed trials. This feedback was provided in February 2010.

At that time DAARP generally agreed with the proposed trial design in PsA (primary endpoints of American College of Rheumatology 20% improvement response criteria (ACR20) at Week 12 and modified Total Sharp Score (mTSS) at Week 24. The sponsor proposed an initial supplemental application that would include ACR20 and health assessment questionnaire-disability index (HAQ-DI) results and a second application with radiographic outcome results and more extended duration (Week 48) ACR20 and HAQ-DI results. DAARP relayed SEALD comments regarding the (b) (4)

At the pre-sBLA meeting for the PsA and AxSpA indications on July 31, 2012, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) agreed that the PsA trial and endpoints appeared to be generally reasonable. Additional detailed discussion took place regarding the analysis of the radiographic endpoint and approaches to handling missing data and extrapolating placebo data for the Week 48 timepoint. Based on their review of the radiographic data, the sponsor proposed to provide post-hoc analyses using an 8 week minimum time interval between radiographs and other imputation methods that were not pre-specified. UCB was allowed to submit all analyses and this would be a review issue.

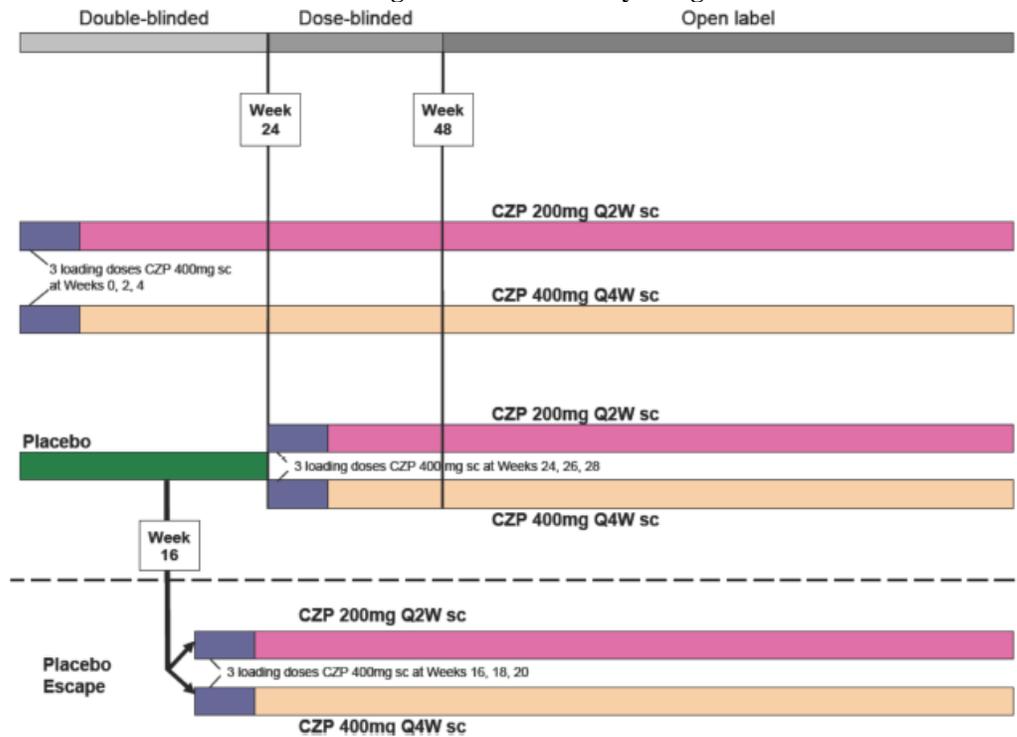
### **III. Summary of Clinical Data in the Submission**

#### **A) Clinical studies supporting PsA**

The doses selected for study in PsA were based on the doses evaluated and shown to be safe and effective for the treatment of patients with RA. A single study in PsA, PsA001, was conducted. This was a multicenter randomized double-blind placebo-controlled study in 393 patients. The study was designed with a 24-week controlled period, where patients received certolizumab 400 mg subcutaneously (sc) at Weeks 0, 2 and 4, followed by 200 mg sc every 2 weeks or 400 mg every 4 weeks or placebo. Placebo group patients who had not achieved an at least 10% improvement in the number of tender and swollen joints were re-randomized at Week 16 to receive certolizumab at either the 200 mg every 2 week or 400 mg every 4 week regimens (following the 400 mg loading doses at Weeks 16, 18, and 20).

The data cutoff for this submission was May 31, 2012. This submission contains the completed placebo-controlled double-blind treatment period with additional safety data through the data cutoff. Although data from the dose-blind treatment period (through Week 48) are complete, these have not been submitted for review in this application.

**Figure 1: PsA001 Study Design**



CZP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks; sc=subcutaneous

The two primary efficacy endpoints in PsA001 were the proportion of ACR20 responders at Week 12 and the change from baseline in modified total Sharp score (mTSS) at Week 24. The key secondary efficacy endpoints were proportion of ACR20 responders at Week 24, change from baseline in HAQ-DI at Week 24, change from baseline in mTSS at Week 48, and proportion of PASI75 responders at Week 24 in the subgroup of patients with psoriasis involving at least 3% body surface area (BSA) at baseline.

Table 1 below summarizes the results for the primary endpoint of ACR20 responders at Week 12. Both the 200 mg Q2W and 400 mg Q4W dose regimens resulted in approximately 30% more ACR20 responders compared with placebo treatment. This treatment effect size is similar to that observed with other TNF inhibitors.

**Table 1: Primary Endpoint: Proportion of ACR20 Responders at Week 12**

	<b>PBO</b>	<b>CZP 200mg Q2W</b>	<b>CZP 400mg Q4W</b>	<b>CZP 200mg Q2W+CZP 400mg Q4W</b>
<b>Week 12</b>	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>	<b>N=273</b>
Responders (%) 95% CI <sup>a</sup>	24.3 (17.1, 31.5)	58.0 (49.7, 66.2)	51.9 (43.4, 60.3)	54.9 (49.0, 60.8)
Difference to PBO <sup>b</sup> (%) 95% CI	–	33.7 (22.8, 44.6)	27.6 (16.5, 38.7)	30.7 (21.4, 40.0)
p-value	–	<0.001	<0.001	<0.001

ACR20=American College of Rheumatology 20% response criteria; CI=confidence interval; CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; “–”=not applicable  
Note: Nonresponder Imputation was used: subjects who withdrew for any reason or placebo subjects who used escape medication were considered as nonresponders from the time that they dropped out or when escape therapy was initiated. Subjects who had missing data at a visit were counted as a nonresponder for the respective visit.

<sup>a</sup> Asymptotic Wald confidence limits.

<sup>b</sup> Treatment difference: CZP 200mg Q2W–PBO, CZP 400mg Q4W–PBO and CZP 200mg Q2W+CZP 400mg Q4W–PBO (and corresponding 95% CI and p-value) were estimated using a standard 2-sided Wald asymptotic test with a 5% alpha level. The corresponding 95% CI for the differences were constructed using their asymptotic standard errors (asymptotic Wald confidence limits).

Data source: PsA001 Week 24 CSR Table 4.2.1

For the other primary endpoint of mean change from baseline to week 24 in mTSS, the pre-specified primary analyses using linear extrapolation for missing data (56 subjects were missing radiographic data from one or more visits) resulted in what the sponsor called “physiologically implausible” changes in mTSS. These results are summarized in Table 2 below. Notably, even with the “physiologically implausible” reduction in mTSS, the difference between either CZP group and placebo was not statistically significant.

**Table 2: Radiographic Primary Endpoint-Pre-Specified Analysis Results**

Change from Baseline in mTSS at Week 24 - Primary Analysis with ANCOVA  
Population: RS [imputation]

Treatment	Change from Baseline		Difference to PBO in Change from Baseline		
	LS Mean (SE) [b]	95% CI [b]	LS Mean (SE) [b]	95% CI [b]	p-value [b]
PBO N=136 [a]	28.92 ( 7.73)	( 13.73, 44.11)			
CZP 200mg N=138	11.52 ( 7.59)	( -3.40, 26.45)	-17.40 ( 9.63)	(-36.32, 1.52)	0.071
CZP 400mg N=135	25.05 ( 7.92)	( 9.48, 40.61)	-3.88 ( 9.65)	(-22.86, 15.10)	0.688
CZP 200mg+400mg N=273	18.28 ( 6.07)	( 6.34, 30.23)	-10.64 ( 8.35)	(-27.05, 5.77)	0.203

Source: Table 4.9.1 of the PsA001 Study Report

However, the “physiologically implausible” changes were a reason the sponsor gave for performing post-hoc analyses where missing data were imputed using median change in the entire population (which was 0) and a minimum 8-week window between radiographs. The results of pre-specified, per-protocol, and post-hoc analyses are summarized in Table 3 below. In the main post-hoc analysis shown in Table 3, the difference between the CZP 200 mg Q2W group and the placebo group was statistically significant, but this was not true for the CZP 400

mg Q4W group. Although the CZP 200 mg Q2W group consistently showed numerical improvement compared with placebo, in multiple other sensitivity analyses, this difference was not statistically significant either. Thus whether radiographic results merit inclusion in the label, and if so, which analyses are most appropriate, will be a major focus of the efficacy review.

**Table 3: Comparison of results of the mTSS change from Baseline to Week 24 using pre-specified, per-protocol, and post-hoc analyses**

	Placebo N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mgQ2W+ CZP 400mg Q4W N=273
<b>SAP-predefined primary analysis (Population: RS)</b> Imputation included linear extrapolation and slotting approach without a specified minimum window between radiograph time points. For subjects with 1 or 0 radiographs, 0 was used for Baseline and 365.5 was used for Week 24.				
LS mean (SE)	28.92 (7.73)	11.52 (7.59)	25.05 (7.92)	18.28 (6.07)
<b>SAP-predefined analysis utilizing CZP data for placebo-escape subjects (Population: RS)</b> Imputation included linear extrapolation and slotting approach without a specified minimum window between radiograph time points. For subjects with 1 or 0 radiographs, 0 was used for Baseline and 365.5 was used for Week 24.				
LS mean (SE)	24.87 (7.39)	12.78 (7.26)	26.50 (7.57)	19.64 (5.81)
<b>Observed Case (Population: RS with Observed Cases)</b> Analysis included slotting approach without a specified minimum window between radiograph time points. Placebo mean change value is biased because it includes only subjects who performed well on placebo therapy (ie, did not escape to CZP).				
Mean (SD)	n=58 0.13 (0.39)	n=126 -0.04 (0.64)	n=118 0.07 (0.69)	n=244 0.01 (0.66)
<b>Post-hoc imputation (Population: RS)</b> Imputation included linear extrapolation using median change from Baseline to Week 24 for subjects with less than 2 radiographs and a minimum 8-week window was specified between radiographs.				
LS mean (SE)	0.28 (0.07)	0.01 (0.07)	0.11 (0.08)	0.06 (0.06)

ANCOVA=analysis of covariance; CZP=certolizumab pegol; LS=least square; mTSS=modified total Sharp score; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; SAP=statistical analysis plan; SD=standard deviation; SE=standard error; TNF $\alpha$ =tumor necrosis factor

Note: All analyses used an ANCOVA model with treatment, region, and prior TNF $\alpha$  exposure (yes/no) as factors and Baseline score as covariate.

Data sources: PsA001 Week 24 CSR [Table 4.9.1](#), [Table 4.10.1](#), [Post-hoc Table 4.17.2.1](#), [Post-hoc Table 4.9.1.1](#)

HAQ-DI is a major secondary endpoint, historically utilized to support a claim of improvement in physical function. Results for the HAQ-DI are summarized in Tables 4 and 5 below. For both mean change from baseline to Week 24 and the proportion of patients achieving an improvement of at least 0.3 units, certolizumab treatment was associated with a statistically significant improvement compared to placebo treatment.

**Table 4: Change from baseline to Week 24 in HAQ-DI (ITT population)**

	<b>PBO<sup>a</sup></b>	<b>CZP 200mg Q2W</b>	<b>CZP 400mg Q4W</b>	<b>CZP 200mg Q2W+ CZP 400mg Q4W</b>
<b>Week 24</b>	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>	<b>N=273</b>
<b>Change from Baseline</b>				
LS mean (SE) <sup>b</sup>	-0.19 (0.05)	-0.54 (0.05)	-0.46 (0.05)	-0.50 (0.04)
95% CI <sup>b</sup>	-0.29, -0.09	-0.64, -0.44	-0.56, -0.36	-0.58, -0.42
<b>Difference to PBO</b>				
LS mean (SE) <sup>b</sup>	–	-0.35 (0.06)	-0.26 (0.06)	-0.31 (0.06)
95% CI <sup>b</sup>	–	-0.47, -0.22	-0.39, -0.14	-0.42, -0.20
p-value <sup>b</sup>	–	<0.001	<0.001	<0.001

CI=confidence interval; CZP=certolizumab pegol; HAQ-DI=Health Assessment Questionnaire-Disability Index; LS=least square; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; SE=standard error; TNF $\alpha$ =tumor necrosis factor alpha; “–“=not applicable

Note: Last Observation Carried Forward was used: for subjects who withdraw for any reason, subjects with a missing Week 24 measurement, or placebo subjects who used escape medication, last observation prior to the early withdrawal or Week 24 or before receiving CZP was carried forward to Week 24.

<sup>a</sup> For the entire placebo group, last observation prior to escape was carried forward to Week 24 for subjects escaping to CZP.

<sup>b</sup> Analysis of covariance model with treatment, region, and prior TNF $\alpha$ -antagonist exposure (yes/no) as factors and Baseline score as a covariate.

Data source: PsA001 Week 24 CSR [Table 4.20.1](#)

**Table 5: HAQ-DI Responders ( $\geq 0.3$  unit improvement)**

	PBO <sup>a</sup>	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W+ CZP 400mg Q4W
<b>MCID <math>\geq 0.3</math> points</b>	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>	<b>N=273</b>
<b>Week 12</b>				
Responders, n (%)	29 (21.3)	63 (45.7)	66 (48.9)	129 (47.3)
Difference to PBO <sup>b</sup> , % (95% CI)	–	24.3 (13.5, 35.1)	27.6 (16.7, 38.5)	25.9 (16.8, 35.0)
p-value	–	<0.001	<0.001	<0.001
<b>Week 24</b>				
Responders, n (%)	21 (15.4)	68 (49.3)	65 (48.1)	133 (48.7)
Difference to PBO <sup>b</sup> , % (95% CI)	–	33.8 (23.5, 44.2)	32.7 (22.3, 43.1)	33.3 (24.8, 41.8)
p-value	–	<0.001	<0.001	<0.001

CI=confidence interval; CZP=certolizumab pegol; HAQ-DI=Health Assessment Questionnaire-Disability Index; MCID=minimal clinically important difference; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; “–”=not applicable

Note: Nonresponder Imputation (NRI) was used: subjects who withdrew for any reason or placebo subjects who used escape medication were considered as nonresponders (ie, not reaching MCID criteria) from the time that they dropped out or when escape therapy was initiated. Subjects who had missing data at a visit were counted as a nonresponder for the respective visit.

<sup>a</sup> For the entire placebo group, NRI was used for subjects escaping to CZP.

<sup>b</sup> Treatment difference: CZP 200mg Q2W–PBO, CZP 400mg Q4W–PBO and CZP 200mg Q2W+CZP 400mg Q4W–PBO (and corresponding 95% CI and p-value) were estimated using a standard 2-sided Wald asymptotic test with a 5% alpha level. The corresponding 95% CI for the differences were constructed using their asymptotic standard errors (asymptotic Wald confidence limits).

Data source: PsA001 Week 24 CSR [Table 4.57](#)

### C) Brief Summary of Safety

The bulk of the safety experience with certolizumab has been in the approved indications of Crohn’s disease and RA. This experience has been evaluated on an ongoing basis via mandated postmarketing safety assessments as part of the REMS and as part of Section 915 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). The safety profile of certolizumab has been consistent with the safety profile of other TNF inhibitors. In this application, the sponsor has focused on the PsA safety database, with a separate discussion of the accrued safety in other indications. The exposure in PsA is summarized in Table 6 below.

**Table 6: Duration of Exposure in the PsA All CZP Safety Pool**

	CZP 200mg Q2W N=197	CZP 400mg Q4W N=196	All CZP N=393
<b>Total study drug duration of exposure<sup>a</sup></b>	<b>n (%) [patient years]</b>	<b>n (%) [patient years]</b>	<b>n (%) [patient years]</b>
>0 months	197 (100.0) [224]	196 (100.0) [219]	393 (100.0) [443]
>6 months	182 (92.4) [220]	176 (89.8) [214]	358 (91.1) [434]
>12 months	139 (70.6) [186]	140 (71.4) [187]	279 (71.0) [373]
>24 months	1 (0.5) [2]	4 (2.0) [8]	5 (1.3) [10]
<b>Duration of exposure<sup>b</sup></b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
<3 months	8 (4.1)	12 (6.1)	20 (5.1)
≥3 to <6 months	7 (3.6)	8 (4.1)	15 (3.8)
≥6 to <12 months	43 (21.8)	36 (18.4)	79 (20.1)
≥12 to <18 months	95 (48.2)	109 (55.6)	204 (51.9)
≥18 to <24 months	43 (21.8)	27 (13.8)	70 (17.8)
≥24 months	1 (0.5)	4 (2.0)	5 (1.3)

CZP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks; SS=Safety Set

Note: The CZP 200mg Q2W and CZP 400mg Q4W groups in the All CZP Safety Pool include subjects escaping from placebo to CZP at Week 16 and subjects switching from placebo to CZP at Week 24.

<sup>a</sup> Total study drug duration is the sum of each subject's study drug duration within a treatment group.

<sup>b</sup> A subject's study drug duration=(date of last dose–date of first dose)+1 maintenance dosing interval (either 14 or 28 days) except where a change of treatment occurred prior to the completion of this period.

Data Source: PsA001 (data cutoff 31 May 2012) [Table 7.1:2](#), [Table 7.1:3](#)

Consistent with the known safety profile of certolizumab and other TNF inhibitors, certolizumab treatment was associated with an increased incidence of AEs, SAEs, discontinuations due to AEs, and death compared to placebo treatment in the 24-week double-blind controlled period (Table 7, below).

Four additional deaths occurred in the dose-blinded period—breast cancer in a 66 yo female on CZP 200 mg Q2W, sepsis in a 59 yo male on 400 mg Q4W, lymphoma in a 69 yo female on 400 mg Q2W and acute myocardial infarction in a 52 yo male on 200 mg Q2W.

During the 24-week controlled period, 1 malignancy (cervical CA) was reported in 1 patient in the CZP 400 mg Q4W group. The sponsor reported 1 additional malignancy (breast CA) in a placebo patient after the data cut-off. During the dose-blind and OLE periods, 4 malignancies were reported—2 events of breast CA, 1 lymphoma, and 1 thyroid neoplasm.

Serious infections were increased in the CZP groups (4 events) compared to placebo (1 event) during the controlled period. TB screening was enacted in the study and no patients seroconverted during the 24-week controlled period. Eight patients had

either positive PPD or a diagnosis of latent/active TB as of the data cutoff.

**Table 7: Summary of Adverse Events (AEs) in the 24-week Double-Blind Treatment Period of PSA001**

	PBO <sup>a</sup>	CZP 200mg Q2W	CZP 400mg Q4W	All CZP <sup>b</sup>
	N=136	N=138	N=135	N=332
	n (%)	n (%)	n (%)	n (%)
Any TEAEs	92 (67.6)	94 (68.1)	96 (71.1)	207 (62.3)
TEAEs by intensity:				
Mild	74 (54.4)	78 (56.5)	77 (57.0)	168 (50.6)
Moderate	49 (36.0)	47 (34.1)	45 (33.3)	99 (29.8)
Severe	2 (1.5)	7 (5.1)	7 (5.2)	15 (4.5)
Drug-related <sup>c</sup> TEAEs	37 (27.2)	39 (28.3)	41 (30.4)	86 (25.9)
Serious TEAEs	6 (4.4)	8 (5.8)	13 (9.6)	22 (6.6)
Discontinuation due to TEAEs:				
Permanent discontinuation	2 (1.5)	4 (2.9)	6 (4.4)	10 (3.0)
Temporary discontinuation	19 (14.0)	30 (21.7)	25 (18.5)	56 (16.9)
Death	0	1 (0.7)	1 (0.7)	2 (0.6)

CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SS=Safety Set; TEAE=treatment-emergent adverse event

<sup>a</sup> For the entire placebo group, CZP data from placebo subjects were not utilized.

<sup>b</sup> The All CZP column includes CZP 200mg Q2W, CZP 400mg Q4W, and the escaped placebo subjects with their CZP data.

<sup>c</sup> Drug-related TEAEs are those with a relationship of “related,” “possibly related,” or those with missing responders.

Data sources: PsA001 Week 24 CSR [Table 8.1](#), [Table 8.6](#), [Table 8.7](#), [Table 8.8](#)

Thus the safety profile of certolizumab in PsA preliminarily appears to be consistent with the overall safety profile of certolizumab and with other TNF inhibitors.

#### IV. Proposed Labeling

Table 7 below contains a summary of approved and proposed labeling for biologic products intended for the treatment of psoriatic arthritis. Remicade was approved for PsA in May 2005, Enbrel was approved for PsA in January 2002, Humira was approved for PsA in October 2005, and Simponi was approved for PsA as part of its original approval in RA, PsA, and Ankylosing Spondylitis (AS) in April 2009. On preliminary review, the major labeling issues are likely to pertain to the following:

1) Dose—the sponsor proposes (b) (4) 200 mg Q2W is the default maintenance dose in RA (but 400 mg Q4W can also be considered). Review will need to evaluate whether there is adequate rationale to support (b) (4)

2) Radiographic results— (b) (4)

(b) (4)  
 3) (b) (4)

4) PRO results for (b) (4)

**Table 8: Approved and Proposed Labeling Claims for PsA**

Efficacy Claims in Currently Approved Labels of Recent (>1998) Products Approved/Proposed for PsA						
	Remicade	Enbrel	Humira	Simponi	Stelara	Cimzia
ACR 20/50/70 Responses	X	X	X	X		(b) (4)
Time course of response				X		
Open-label maintenance	X		X			
Improvmnts as early as week 2	X			X (wk 4)		
Similar responses in subtypes	X					
ACR components	X	X	X	X		
Radiographic response	X	X	X			
Proportion of nonprogressors	X					
Open-label maintenance		X	X			
Physical function						
HAQ-DI	X	X	X	X		
SF-36	X	X	X			
Open-label maintenance	X		X			(b) (4)
Dactylitis/Enthesitis	X			X		
PASI 50/75/90 Responses	X (75/90)	X (50/70)	X (75/90)			
Open-label maintenance	X	X				
Morning Stiffness		X				(b) (4)
Number of studies	1	1	2	1	2	1
Prev or concurrent psoriasis approval	Yes	Yes	Yes	No	Yes	No
Prev or concurrent RA approval	Yes	Yes	Yes	Yes	No	Yes

## V. Conclusions

This application is fileable from a clinical perspective. Filing checklist is appended to this memorandum.

This application should be reviewed under that Standard review timeline.

- The expectations for a priority review designation would be that the application represents a drug with the potential to provide a significant advance in treatment, such as evidence of increased effectiveness, substantial reduction of a treatment-limiting drug reaction, or documented enhancement of patient willingness or ability to take the drug according to the required schedule and dose. Based on this preliminary review, this application would not qualify for priority review.

Because of its relatively recent original approval, global/multicenter nature of the trials, and the extremely low likelihood of impacting overall conclusions, a routine inspection by the Division of Scientific Investigations (DSI) is unlikely to be informative and will not be requested.

Based on preliminary review, this application does not appear to warrant an advisory committee (AC) meeting. The efficacy of certolizumab for clinical responses in PsA appears to be similar to other approved TNF inhibitors. Although the radiographic data are a major issue, this would likely have more of an impact on labeling rather than approval.

## VI. Comments to Sponsor for the 74-day letter:

Based on our filing review, we have identified the following issues:

### 1) Radiographic data

[Redacted] (b) (4)

### 2)

[Redacted] (b) (4)

### 3) Patient Reported Outcomes (PROs) for

[Redacted] (b) (4)

Additionally, the proposed PROs [Redacted] (b) (4)

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SARAH K YIM  
01/17/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125160Origs213**

**CHEMISTRY REVIEW(S)**



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

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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- $\alpha$ . 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 [REDACTED] (b) (4) 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 [REDACTED] (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

cc:

Andrew Shiber	HFD-123
S. Muthukkumar	HFD-123
R. Rawat	HFD-123
DMA Drive	BLA 125160
DMA Paper files	BLA 125160/213 and 215

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/s/  
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SUBRAMANIA MUTHUKKUMAR  
09/21/2013

RASHMI RAWAT  
09/23/2013

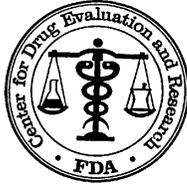
SARAH B KENNETT  
09/23/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125160Origs213**

**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 #:** BLA 125160

**Drug Name:** Cimzia (certolizumab pegol)

**Indication(s):** Treatment of adult patients with active psoriatic arthritis

**Applicant:** UCB, Inc.

**Date(s):** Receipt date: November 29, 2012  
PDUFA date: September 29, 2013 (actual day September 27, 2013)

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics II

**Statistical Reviewer:** Kiya Hamilton, Ph.D.

**Concurring Reviewers:** Ruthanna Davi, Ph.D., Statistical Reviewer

**Medical Division:** Division of Pulmonary, Allergy and Rheumatology Products

**Clinical Team:** Suzette Peng, M.D., Medical Reviewer  
Sarah Yim, M.D., Team Leader  
Badrul A. Chowdhury, M.D. Ph.D., Medical Division Director.

**Project Manager:** Nina Ton

**Keywords:** BLA, clinical studies, multiplicity, sensitivity analyses

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## 1 EXECUTIVE SUMMARY

With this submission, UCB Pharma, Inc. is proposing CIMZIA<sup>®</sup> (CZP) for the treatment of adults with active Psoriatic Arthritis (PsA). UCB is requesting approval for dosage strength of CZP 200mg every two weeks (Q2W) [REDACTED] Study PsA001 is provided by the applicant in support of this proposal. The applicant conducted study PsA001 with the primary objective of demonstrating the efficacy of CZP administered subcutaneously (SC) at the dose of 200mg every two weeks or 400mg every 4 weeks after loading with 400mg at weeks 0, 2 and 4 on the signs and symptoms of active PsA and on the inhibition of progression of structural damage in adults with active PsA.

Based on study PsA001, the first primary efficacy endpoint, ACR20 at week 12 demonstrated statistically significant effects for both CZP 200mg Q2W and CZP 400mg Q4W compared to placebo. However, the pre-defined analysis for the second primary efficacy endpoint, change from baseline in mTSS at week 24, did not demonstrate statistically significant effects for either of the CZP doses compared to placebo. This was at least partially due to the SAP pre-defined imputation rules put in place by the applicant, which led to an unusually high score being imputed for missing mTSS data. Post-hoc FDA-defined sensitivity analyses were conducted to explore the impact of various assumptions regarding the missing data on the treatment effect. Analyses excluding subjects with less than two available radiographs and in one case, utilizing the placebo escaped data while in the other case simply excluding these placebo subjects, both demonstrated statistically significant effects on mTSS for CZP 200mg Q2W relative to placebo. With these analyses, the CZP 400 mg Q4W group was not statistically significantly different from placebo; however, the numerical estimates of the treatment effect did trend in the same direction as the CZP 200mg Q2W group favoring CZP over placebo. For the major secondary efficacy endpoints, HAQ-DI at week 24 and PASI75 at week 24 each of the individual dose groups, CZP 200mg Q2W and CZP 400mg Q4W, were statistically significantly different from placebo. Conclusions for these two endpoints are not sensitive to the methods applied for missing data; however these results could be criticized for not being accurately accounted for in the multiplicity plan (i.e., analyzing the pooled dose groups versus placebo was pre-specified while the regulatory interest is primarily in comparing each dose group to placebo).

No statistically significant differences in the treatment effect in terms of the primary efficacy endpoints across gender, race, age or geographic region categories were identified.

## 2 INTRODUCTION

### 2.1 Overview

#### 2.1.1 Class and Indication

CIMZIA (certolizumab pegol (CZP)) is currently FDA approved for Crohn's disease and Rheumatoid Arthritis (RA). In the current submission, UCB Pharma, Inc. proposes CIMZIA for the treatment of adults with active Psoriatic Arthritis (PsA). UCB is requesting approval for dosage strength of CZP 200mg every two weeks (Q2W) [REDACTED] (b) (4)

#### 2.1.2 History of Drug Development

UCB Pharma, Inc. had some interactions with the Division of Pulmonary, Allergy, and Rheumatology Products to discuss Cimzia for their PsA and axial spondyloarthritis (ASpA) programs (under IND 009869). Pertinent parts of the statistical portion of the communications and interactions for the Cimzia PsA program are summarized herein.

UCB Pharma, Inc. requested a Type B meeting on March 9, 2009 to discuss the PsA indication. Written responses were provided in February 2010 by the Division in response to this Type B meeting request. UCB was seeking feedback on the inclusion of certain endpoints in Study PsA001 in support of their proposed indication and labeling claims. The Division responded that

all endpoints and comparisons [REDACTED] (b) (4)  
[REDACTED] This must include details regarding how the overall significance level for the study will be protected for all sources of multiplicity in the planned tests.

UCB Pharma, Inc. was also seeking advice on their proposed analyses of ACR20 and mTSS at weeks 24 and 48, as well as, how to handle patients who withdraw from the study early. Their proposal for data up to week 24 was as follows:

- For the mTSS analysis at Week 24, subjects who withdraw and have radiographs taken before their early withdrawal will have their scores utilized by linear extrapolation
- For the ACR20 analysis at Week 24, subjects who withdraw for any reason or use rescue medication will be considered as non-responders from the time that rescue therapy was initiated
- For the ACR20 analysis at Week 24, subjects who have missing data at a visit will be counted as a non-responder for the respective visit

The Division found these approaches to be generally acceptable. The Division suggested that instead of using the Full Analysis Set for the primary efficacy analyses, which excluded patients who were randomized and received treatment but were missing efficacy assessments, to use the Randomized Set of all randomized patients.

On November 22, 2011 the Division responded to UCB Pharma, Inc.'s request for addition information on the proposed mTSS analysis. The Division suggested that UCB Pharma, Inc.

collect radiographic data at week 24 regardless of whether patients withdrew from treatment or enter escape therapy and to conduct sensitivity analysis using these data (i.e. retrieved dropout). The Division also stated that given UCB Pharma, Inc.'s patient enrollment was completed and some patients may have already had their final visit, that it may not be feasible to collect such data. Also, the Division suggested that UCB Pharma, Inc. conduct an additional sensitivity analysis to examine the proportions of patients with  $\leq 0$  change from baseline in mTSS at week 24; in this analysis patients who discontinued or entered escape therapy should be classified as non-responders.

A pre-sBLA meeting was held on July 31, 2012, to discuss the applicant's post-hoc analysis to support the use of Cimzia in the treatment of PsA. The Division raised concerns regarding the applicant's imputation method applied in the post-hoc analyses for mTSS since this is based on the unblinded data. The Division told the applicant that this is a review issue. The applicant also suggested the addition of a minimum time interval between measurements in radiographs of 8 weeks be used in the week 24 post-hoc analyses of mTSS. The Division told the applicant:

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.

There was also discussion of the applicant wanting to use the observed data versus the randomized set for the analysis of the radiographic endpoint. In general, the Division does not recommend excluding patients from the analysis since this may introduce bias and influence the results. Also, excluding patients from the analysis may not preserve the baseline comparability between treatment groups achieved by randomization. We recommended again that UCB evaluate the proportion of patients with no progression as a sensitivity analysis. We 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 therapy will be considered non-responders. The Division stated the following.

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.

Note there was no discussion in any of the meetings regarding the applicant combining the two Cimzia doses to analyze any of the endpoints.

### **2.1.3 Specific Studies Reviewed**

Study PsA001 is the focus of this review. Study PsA001 is a phase 3, randomized, double-blind, parallel-group, multi-center, placebo-controlled study in male and female patients at least 18 years of age at screening with adult-onset active and progressive PsA.

## 2.2 Data Sources

The study report including the protocol and the statistical analysis plan for study PsA001 were utilized in the review of this submission. All data was supplied by the applicant to the CDER electronic data room in SAS transport format. The data and final study report for the electronic submission were archived under the network path location <http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea68112c9b5>.

The information needed for this review was contained in modules 1, 2.5, 2.7, and 5.

## 3 STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

In general, the submitted study report, protocol, statistical analysis plan, and efficacy data sets for study PsA001 were sufficient in terms of quality and integrity for review. Primary and secondary efficacy analyses for study PsA001 were reproducible from the data sets provided.

### 3.2 Evaluation of Efficacy

#### 3.2.1 Study Design and Endpoints

The summary of the study design and endpoints for the efficacy study is given in **Error! Reference source not found.** Study PsA001 was a Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multi-center study in male and female patients 18 years of age and older. The design and efficacy endpoints are explained in detail in the following paragraphs.

**Table 1 Summary of Study Design**

Study ID	Indication	Length of the Study	Treatment Arms	Number of Patients	Primary Efficacy Endpoints
PsA001	PsA	Period 1: 1 to 5 weeks	CZP 200mg Q2W	138	ACR20 responder at Week 12
			CZP 400mg Q4W	135	
		Period 2: 24 weeks DB	Placebo	136	Change from baseline in mTSS at Week 24
			<i>Placebo early escape at week 16:</i>		
		• CZP 200mg Q2W	30		
		• CZP 400mg Q4W	29		

- DB: double blind treatment period
- Q2W: Every 2 weeks
- Q4W: Every 4 weeks

Study PsA001 was designed to assess the efficacy and safety of CZP administered subcutaneously (SC) in comparison to placebo in patients with PsA. The study consisted of five periods. Period 1 was the screening period, week 1 to week 5. Period 2 was a 24 week double-blind, placebo-controlled treatment period (week 0 to week 24). Period 3 consisted of week 24 to week 48, dose-blinded for the subjects and the investigators (no placebo). Period 4, week 48 to week 158, is the open-label CZP. Period 5 is the safety follow-up period, week 158 to week 166. At the time of this review Periods 1 and 2 were completed and Periods 3, 4 and 5 are on-going. Thus, this review only covers Period 2. Dosage strengths CZP 400mg Q2W at weeks 0, 2 and 4 followed by CZP 200mg Q2W SC starting at week 6, CZP 400mg Q2W at weeks 0, 2 and 4 followed by CZP 400mg Q4W SC starting at week 8 and placebo were studied in study PsA001.

There were two primary endpoints for this study, ACR20 at week 12 and the change from baseline to week 24 in the modified Total Sharp Score (mTSS). ACR20 is defined as the as the proportion of subjects meeting the American College of Rheumatology criteria of 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the remaining 5 core set measures (subject global assessment of pain, subject global assessment of disease activity, physician global assessment of disease activity, subject assessment of physical function and one acute phase reactant value [CRP]). For quantification of the mTSS endpoint, patients were required to have radiographs of both hands and both feet. The applicant used the Sharp-van der Heijde modified scoring method for PsA to assess structural joint damage and its progression in PsA. This scoring quantifies the extent of bone erosions and joint space narrowing for 64 and 52 joints, respectively. Higher scores represent greater damage.

The key secondary endpoints were

- ACR20 responder at week 24
- Change from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) at week 24
- Psoriasis Area and Severity Index 75% response (PASI75 responder) at week 24

Baseline ACR20 was defined as the last valid measurement before the study medication was administered. For baseline mTSS, an x-ray performed up to 2 weeks after baseline was accepted as the baseline measurement.

As per the pre-specified study design, patients receiving placebo were evaluated for escape from study treatment at week 16. Patients receiving placebo who met the escape criteria of being a non-responder at both weeks 14 and 16 were re-randomized in a 1:1 ratio to receive CZP 200mg SC Q2W or CZP 400mg SC Q4W from week 22 onwards after administration of loading doses of CZP 400mg Q2W at weeks 16, 18 and 20. Non-responders were defined as patients having either less than 10% improvement in the number of tender joints or less than 10% improvement in the number of swollen joints or less than 10% improvement in both. Patients in the CZP groups who qualified for escape were not given an opportunity to enter early escape at week 16 and continued with their current treatment. The applicant states that the Interactive Voice Response System (IVRS) was used to qualify patients for early escape at weeks 14 and 16 so that neither patients nor investigators were un-blinded to treatment assignment as a result of this study design feature. Since escaped therapy was not offered until week 16, the primary endpoint, ACR20 at week 12 was not affected.

### **3.2.2 Statistical Methodologies**

The protocol specified that the efficacy analyses were to be performed using the randomized set (RS), defined as all randomized subjects. The protocol specified that the first primary efficacy endpoint, ACR20 responder at week 12, was to be compared between the two individual CZP-treated groups and the placebo group using the standard two-sided Wald asymptotic test at the  $\alpha=0.05$  level. The protocol also indicated that the CZP 200mg Q2W and CZP 400mg Q4W combined group was to be compared to placebo but these results were not considered part of the confirmatory analyses. A secondary analysis was also conducted on ACR20 response using logistic regression with factors for treatment, region and prior TNF-antagonist exposure (Y/N). The treatment effects were estimated using odds ratios. Patients who withdrew early from the study for any reason were considered non-responders from the time they withdrew. Patients with missing ACR20 values at a visit were considered non-responders for that particular visit.

As per protocol, the second primary efficacy endpoint, change from baseline to week 24 in mTSS, was to be compared between the CZP 200mg Q2W and CZP 400mg Q4W combined group versus placebo using the pre-specified analysis of covariance (ANCOVA) model with treatment, region and prior TNF-antagonist exposure as factors and baseline mTSS as covariate. The pre-specified analysis for handling missing mTSS visits was as follows:

Case 1: mTSS was missing at baseline, week 12 and week 24: impute baseline value missing the minimal determined baseline measurement of all subjects; impute week 24 values using the maximal determined week 24 measurements of all subjects; interpolate the week 12 value.

Case 2: mTSS was missing at baseline only: impute by linearly extrapolating week 12 and 24 measurements in the direction of baseline.

Case 3: mTSS was available at baseline only: impute week 24 values using maximal determined week 24 measurements of all subjects; interpolate week 12 measurement.

Case 4: mTSS was missing at week 12 only: impute week 12 value by linearly interpolating baseline and week 24 measurements.

Case 5: mTSS was available at week 12 only: impute baseline value using minimal determined baseline measurement of all subjects; impute week 24 values using maximal determined week 24 measurements of all subjects.

Case 6: mTSS was missing at week 24 only: impute week 24 value by linearly extrapolating baseline and week 12 measurements.

Case 7: mTSS was available at week 24 only: impute baseline value using the minimal determined baseline measurement of all subjects; interpolate week 12 measurement.

Case 8: mTSS was available at baseline, week 12 and week 24 (no imputation).

The applicant stated that the extrapolation and interpolation was done using the scheduled date for week 12 and week 24 and the first injection for baseline. The minimal determined baseline measurement of all the subjects in the RS was 0. The maximal determined week 24 measurement of all subjects in the RS was 356.5. Placebo subjects who escaped early were considered missing from the time point of escape onward for purposes of the analysis of mTSS (i.e., even if the week 24 value was available for an escaped subject, it was ignored and the subject was handled according to four of the rules above, specifically cases 1, 3, 5 and 6). Subjects who withdrew before week 24 and had radiographs taken before their Early Withdrawal Visit were included in the analysis by linearly extrapolating the scores from the last 2 radiographs before week 24. The same pre-specified approach was applied for subjects with a missing 24-week measurement. For placebo subjects who escaped early to CZP, the last 2 scores before receiving CZP were utilized. The visits to be utilized for the extrapolation approach included baseline, week 12, and early withdrawal.

The protocol specified that as a sensitivity analysis, a retrieved dropout approach was also to be conducted for the change from baseline to week 24 in mTSS for placebo subjects who escaped early to CZP. For this analysis, the week 24 mTSS scores of placebo subjects who escaped to CZP were utilized, as observed, for treatment group comparisons. Since placebo patients who escaped were to receive CZP, this imputation should bias the comparison of the treatment groups in the direction of the placebo group appearing more similar the treatment group. This approach was applied to escaped subjects only, since subjects who dropped out, had no week 24 x-ray performed.

The applicant conducted post-hoc analyses of the primary endpoint, mTSS at week 24. The applicant stated that the pre-defined imputation rules led to physiologically implausible changes in mTSS. The post-hoc analysis imputed any missing mTSS values with the median change from baseline in the RS, this value was 0. A minimum time interval of 8 weeks between radiographs was defined to perform linear interpolation or extrapolation. If the radiographs were less than 8

weeks apart, then the second radiograph was considered missing and the imputations rules below were utilized for subjects with one remaining radiograph:

Case 1: mTSS was missing at baseline, week 12 and week 24: impute missing values with the median change from baseline, 0.

Case 2: mTSS was missing at baseline only: impute by linearly extrapolating week 12 and 24 measurements in the direction of baseline. (No change from pre-specified analysis)

Case 3: mTSS was available at baseline only: impute missing values with the median change from baseline, 0.

Case 4: mTSS was missing at week 12 only: impute week 12 value by linearly interpolating baseline and week 24 measurements. (No change from pre-specified analysis)

Case 5: mTSS was available at week 12 only: impute missing values with the median change from baseline, 0.

Case 6: mTSS was missing at week 24 only: impute week 24 value by linearly extrapolating baseline and week 12 measurements. (No change from pre-specified analysis)

Case 7: mTSS was available at week 24 only: impute missing values with the median change from baseline, 0.

Case 8: mTSS was available at baseline, week 12 and week 24 (no imputation). (No change from pre-specified analysis)

The applicant also conducted four post-hoc sensitivity analyses to ensure the results were consistent across the different imputation methods:

1. Imputation of missing values by using mean change from Baseline in entire study population
2. Imputation of missing values by using worst change from Baseline in entire study population
3. Imputation of missing values by using worst change from Baseline in same treatment group
4. Exclusion of subjects with  $\leq 1$  available value.

This review will focus on the pre-specified mTSS analysis and sensitivity analyses on the pre-specified endpoint, not the post-hoc analysis. The post-hoc analyses provided by the applicant were complicated. It is unknown exactly how many post-hoc analyses were actually conducted by the applicant and the ones that were specified above could have been defined after data dredging.

According to the protocol, the ACR20 response at week 24 was to be analyzed using the same method as ACR20 response at week 12. Subjects who withdrew prior to week 24 for any reason were considered non-responders. Subjects who were missing data at week 24 were counted as non-responders for that visit and placebo subjects who escaped early to CZP were considered non-responders from the time the escape medication was initiated.

According to the protocol, the change from baseline in HAQ-DI at week 24 was to be compared between the combined CZP groups (CZP 200mg Q2W and 400mg Q4W) and placebo using an ANCOVA model with baseline HAQ-DI score, treatment group, region and prior TNF $\alpha$  antagonist exposure. The last observation carried forward (LOCF) method was applied to missing post-baseline values. The placebo subjects who escaped early, their last observation prior to escape were carried forward to week 24. The Division generally does not accept LOCF as an imputation strategy because this implies patients who discontinue treatment will have the same outcome over time. This may lead to a biased standard error estimates since we are ignoring inherent uncertainty in the imputed values. In addition, this approach may not be conservative in terms of the patient's imputed outcome. FDA conducted a sensitivity analysis applying baseline observation carried forward (BOCF) for subjects who withdrew for any reason, subjects with missing week 24 measurement or placebo subjects who escaped to CZP. While this analysis is likely to result in a more appropriate imputed outcome for each subject, the criticism of the LOCF approach that the standard error estimates are artificially small remains applicable to the BOCF analysis. Therefore, to supplement the BOCF analysis and to circumvent this missing data issue, a responder analysis and analysis at a time point before escape (i.e., before most missing data has occurred) for the HAQ-DI is also provided.

PASI75 at week 24 was used to investigate the effect of treatment on psoriatic skin disease. As per protocol, only subjects who had psoriasis covering at least 3% of their body surface area at baseline were included in this analysis. Also as per protocol, the applicant compared the combined CZP groups (CZP 200mg Q2W and 400mg Q4W) and placebo using the same statistical methods as the primary endpoint, ACR20 response. Subjects who withdrew before week 24 were considered non-responders. Subjects who had missing data at week 24 were considered non-responders for that visit. The week 16 response for the placebo subjects who escaped early to CZP was utilized from when the escaped medication was initiated.

For study PsA001 the protocol specified the use of a hierarchical testing procedure to account for multiplicity across treatment comparisons and primary and major secondary endpoints. Conditional on the first test being significant, the other primary and the major secondary endpoints were to be tested in the order described below if the previous key endpoint was statistically significant. If the previous major endpoint was not statistically significant, no further comparisons were to be made. All statistical tests were to be two-sided and performed at the 5% alpha level. The predefined order of hypotheses testing was as follows:

1. ACR20 response at Week 12 for CZP 200mg Q2W
2. ACR20 response at Week 12 for CZP 400mg Q4W
3. ACR20 response at Week 24 for CZP 200mg Q2W
4. ACR20 response at Week 24 for CZP 400mg Q4W
5. Change from Baseline in HAQ-DI at Week 24 for CZP 200mg Q2W and CZP 400mg Q4W combined
6. Change from Baseline in mTSS at Week 24 for CZP 200mg Q2W and CZP 400mg Q4W combined
7. PASI75 response at Week 24 for CZP 200mg Q2W and CZP 400mg Q4W combined
8. Change from Baseline in mTSS at Week 48 for CZP 200mg Q2W and CZP 400mg Q4W combined.

Note that this multiplicity plan is not in strict agreement with the definition of the two primary endpoints in that the second primary endpoint, change from baseline in mTSS at week 24 is listed sixth after several secondary endpoints in this plan.

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The summary of the patient disposition in study PsA001 is given in Table 2. There were 409 subjects randomized in a 1:1:1 ratio stratified by center and prior TNF $\alpha$  antagonist exposure. At week 0, 138 were assigned to receive CZP 200mg Q2W, 135 were assigned to receive CZP 400mg Q4W and 136 were assigned to receive placebo. At week 16, 59 (43%) of the placebo subjects met early escape criteria and began receiving CZP (30 subjects were re-randomized to receive CZP 200mg Q2W and 29 subjects received CZP 400mg Q4W). Note there were 39 (10%) subjects in the CZP groups that met the early escape criteria, however, due to the protocol defined escape rules were unable to escape (18 (13%) subjects in the CZP 200mg Q2W group and 21 (16%) subjects in the CZP 400mg Q4W group).

The primary reasons for discontinuations were consent withdrawal (3%) and AEs (3%). The reasons for discontinuations were infrequent and balanced across the treatment groups.

**Table 2 Subject Disposition (RS)**

	Placebo	CZP 200mg Q2W	CZP 400mg Q4W
Subjects Randomized	136	138	135
Discontinued	16 (12%)	10 (7%)	15 (11%)
Reason for early discontinuation			
Adverse event	2 (2%)	4 (3%)	7 (5%)
Lack of efficacy	2 (2%)	0	1 (0.7%)
Protocol violation	0	1 (0.7%)	0
Lost to follow-up	4 (3%)	1 (0.7%)	1 (0.7%)
Consent withdrawn	7 (5%)	2 (1%)	5 (4%)
Other	1 (0.7%)	2 (1%)	1 (0.7%)

Source: Cimzia/Active Psoriatic Arthritis PsA001 Double-Blind-Protocol Number PsA001 Table 1.3, page 69

The demographics and baseline characteristics in study PsA001 are summarized in Table 3 for the RS population. These factors were generally well-balanced across the treatment groups.

**Table 3 Subject Demographic and Baseline Characteristics (RS)**

		<b>Placebo</b>	<b>CZP 200mg Q2W</b>	<b>CZP 400mg Q4W</b>
		<b>N=136</b>	<b>N=138</b>	<b>N=135</b>
Age (years)	Mean ± SD	47.3 ± 11.1	48.2 ± 12.3	47.1 ± 10.8
	Range	22 to 75	19 to 73	22 to 70
Gender [n (%)]	Male	57 (42%)	64 (46%)	62 (46%)
	Female	79 (58%)	74 (54%)	73 (54%)
Race [n (%)]	American Indian/ Alaskan Native	1 (0.7%)	1 (1%)	0
	Asian	1 (0.7%)	0	0
	Black	0	1 (1%)	1 (1%)
	Native Hawaiian/Other Pacific Islander	0	0	0
	White	132 (97%)	135 (98%)	133 (99%)
	Other/Mixed	2 (2%)	1 (1%)	1 (1%)
	Ethnicity [n (%)]	Hispanic or Latino	24 (18%)	24 (17%)
	Not Hispanic or Latino	112 (82%)	114 (83%)	113 (84%)
Weight (kg)	Mean ± SD	82.6 ± 19.9	85.8 ± 17.7	84.8 ± 16.7
	Range	31.1 to 151.6	51.4 to 146.0	54.0 to 144.7
Height (cm)	Mean ± SD	168.2 ± 10.2	167.9 ± 9.98	169.6 ± 8.48
	Range	141.0 to 195.0	148.0 to 193.0	150.0 to 188.0
BMI (kg/m <sup>2</sup> )	Mean ± SD	29.2 ± 6.7	30.5 ± 6.2	29.6 ± 6.55
	Range	15.6 to 63.7	17.9 to 51.1	19.0 to 54.3

Source: Clinical Study Report-Protocol Number PsA001 Table 3, pages 111-113

\*Small amount (<1%) of missing data for certain endpoints ignored in calculations.

### 3.2.4 Results and Conclusions

The results in this section will be shown in the order of the hierarchical test procedure. The pre-specified primary efficacy analysis for the first primary endpoint, ACR20 response at week 12, as provided by the sponsor is shown in Table 4. The proportion of subjects achieving an ACR20 response at week 12 was statistically significantly higher in the both the CZP 200mg Q2W group (58%) and CZP 400mg Q4W group (52%) than the placebo group (24%). There were a higher proportion of subjects achieving an ACR20 response in the CZP 200mg Q2W group than the CZP 400mg Q4W group at week 12.

**Table 4 Primary Efficacy Analysis: ACR20 Response at Week 12 (RS, with Non-Responder Imputation)**

	<b>Placebo</b>	<b>CZP 200mg Q2W</b>	<b>CZP 400mg Q4W</b>
<b>Week 12</b>	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>
<b>Responders (%)</b>	33 (24%)	80 (58%)	70 (52%)
<b>Difference between the treatment groups (p-value)</b>		34% (<0.001)	28% (<0.001)

Source: Clinical Study Report-Protocol Number PsA001 Table 8-2, page 126

Since the by-treatment group comparison for the first primary efficacy endpoint, ACR20 at week 12 was statistically significant for the CZP 200mg Q2W group followed by the CZP 400mg Q4W group and according to the pre-specified multiplicity plan, inferential statistical analysis may proceed to the first major secondary efficacy endpoint, ACR20 response at week 24 for CZP 200mg Q2W.

The pre-specified statistical analysis of the ACR20 response at week 24 is shown in Table 5. The proportion of subjects achieving an ACR20 response at week 24 was statistically significantly higher in the CZP 200mg Q2W group (64%) than in the placebo group (24%). Since this comparison was statistically significant, the inferential statistical analysis may proceed to the next major secondary efficacy endpoint, ACR20 response at week 24 for CZP 400mg Q4W, also shown in Table 5. The proportion of subjects achieving an ACR20 response at week 24 was statistically significantly higher in the CZP 400mg Q4W group (56%) than in the placebo group. Similar to the week 12, the CZP 200mg Q2W group had a greater proportion of subjects who achieved an ACR20 response at week 24 than the CZP 400mg Q4W group.

**Table 5 Secondary Efficacy Analysis: ACR20 Response at Week 24 (RS, with Imputation)**

	<b>Placebo</b>	<b>CZP 200mg Q2W</b>	<b>CZP 400mg Q4W</b>
<b>Week 24</b>	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>
<b>Responders (%)</b>	32 (24%)	88 (64%)	76 (56%)
<b>Difference between the treatment groups (p-value)</b>		40% (<0.001)	28% (<0.001)

Source: Clinical Study Report-Protocol Number PsA001 Table 8-8, page 139

Continuing on with the hierarchical testing procedure, since the by-treatment group comparisons for the first primary efficacy endpoint and the first major secondary efficacy endpoint were statistically significant, inferential statistical analysis may continue to the next major secondary efficacy endpoint, the change from baseline in HAQ-DI score at week 24 for CZP 200mg Q2W and 400mg Q4W combined. The pre-specified statistical analysis of the HAQ-DI for the combined CZP groups as well as the results for the individual CZP 200mg Q2W and CZP 400mg Q4W groups are shown in Table 6. Although the protocol specified that the combined CZP group was to be compared to placebo, for this review emphasis will be placed on the individual CZP group results rather than the CZP combined group results because of the regulatory interest

in the individual doses. Strictly speaking this is not in accordance with the pre-specified multiplicity plan; however, this approach is not expected to have seriously inflated the type I error in that the results for the combined group versus placebo were generally favorable as well. LOCF was used for subjects who withdrew for any reason, subjects with a missing week 24 measurement, or placebo subjects who used escape medication. The last observation prior to the early withdrawal or week 24 or before receiving CZP was carried forward to Week 24. The last observation prior to escape for the placebo patients was carried forward to week 24 for subjects escaping to CZP. The results of the FDA sensitivity analysis applying BOCF for subjects who withdrew for any reason, subjects with missing week 24 measurement or placebo subjects who escaped to CZP is shown in Table 7 for the change from baseline in HAQ-DI at week 24. Additional sensitivity analyses, including a responder analysis (where responder is defined as a change from baseline in HAQ-DI of at least 0.3) and analysis of the HAQ-DI using the protocol defined statistical procedures but at week 12, before escape occurred, are provided in Tables 8 and 9, respectively. Results of each of these sensitivity analyses are consistent with one another as well as with the protocol-defined analysis incorporating LOCF imputation in indicating that there is a significant benefit for each of CZP 200 mg Q2W and CZP 400 mg Q4W over placebo for HAQ-DI.

The mean change from baseline in HAQ-DI at week 24 was greater for both the CZP 200mg Q2W group (-0.54) and the CZP 400mg Q4W group (-0.46) than for the placebo group (-0.19). The comparison to placebo was statistically significant for both the CZP 200mg group and the CZP 400mg Q4W group. The CZP 200mg Q2W group had a slightly greater mean change from baseline than the CZP 400mg Q4W group. The CZP 200mg Q2W group also had a numerically greater difference from placebo than CZP 400mg Q4W group.

**Table 6 Change from Baseline in HAQ-DI at Week 24 (RS, LOCF Imputation)**

	<b>Placebo</b>	<b>CZP 200mg Q2W</b>	<b>CZP 400mg Q4W</b>	<b>CZP 200mg Q2W + CZP 400mg Q4W</b>
<b>Week 24</b>	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>	<b>N=273</b>
<b>Change from Baseline LS Mean (SE)</b>	0.19 (0.05)	-0.54 (0.05)	-0.46 (0.05)	-0.5 (0.04)
<b>Difference from Placebo (p- value)</b>		-0.4 (<0.001)	-0.3 (<0.001)	-0.3 (<0.001)

Source: Clinical Study Report-Protocol Number PsA001 Table 8-9, page 143

**Table 7 Reviewer Analysis: Change from Baseline in HAQ-DI at Week 24 (RS, BOCF Imputation)**

	Placebo	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W + CZP 400mg Q4W
<b>Week 24</b>	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>	<b>N=273</b>
<b>Change from Baseline LS Mean (SE)</b>	0.16 (0.05)	-0.53 (0.05)	-0.46 (0.05)	-0.5 (0.04)
<b>Difference from Placebo (p-value)</b>		-0.4 (<0.001)	-0.3 (<0.001)	-0.3 (<0.001)

**Table 8 HAQ-DI Responders at Weeks 12 and 24 (RS, with Nonresponder Imputation)**

	Placebo	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W + CZP 400mg Q4W
<b>MCID≥0.3 points</b>	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>	<b>N=273</b>
<b>Week 12</b>				
<b>Responders (%)</b>	29 (21%)	63 (46%)	66 (49%)	129 (47%)
<b>Difference between the treatment groups (p-value)</b>		24% (<0.001)	28% (<0.001)	26% (<0.001)
<b>Week 24</b>				
<b>Responders (%)</b>	21 (15%)	68 (49%)	65 (48%)	133 (49%)
<b>Difference between the treatment groups (p-value)</b>		34% (<0.001)	33% (<0.001)	33% (<0.001)

Source: Clinical Study Report-Protocol Number PsA001 Table 8-10, page 145

**Table 9 Reviewer Analysis: Change from Baseline in HAQ-DI at Week 12 (RS, with LOCF Imputation)**

	Placebo	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W + CZP 400mg Q4W
<b>Week 12</b>	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>	<b>N=273</b>
<b>Change from Baseline LS Mean (SE)</b>	-0.19 (0.04)	-0.48 (0.04)	-0.42 (0.05)	-0.46 (0.03)
<b>Difference from Placebo (p-value)</b>		-0.30 (<0.001)	-0.24 (<0.001)	-0.27 (<0.001)

Since the by-treatment group comparisons for the first primary efficacy endpoint and pre-selected major secondary efficacy endpoints were statistically significant and according to the pre-specified multiplicity plan, inferential statistical analysis may continue to the second primary efficacy endpoint, the change from baseline in mTSS at week 24 for CZP 200mg Q2W and 400mg Q4W combined. For the reasons previously described (section 3.2.2), this review places emphasis on the results of the pre-specified analysis rather the post-hoc analysis. Despite that the pre-specified analysis was to compare the pooled CZP dose groups with placebo, emphasis will be placed on the comparisons of each of the individual CZP groups to placebo because of the regulatory interest in the individual doses.

Table 10 shows the results from the applicant's pre-specified analysis of the second primary efficacy endpoint, change from baseline in mTSS at week 24 in the RS population with the applicant's pre-defined missing data imputation and not utilizing the placebo escaped subjects CZP data. The mean change from baseline in mTSS at week 24 was not statistically significant in either the CZP 200mg Q2W group ( $p=0.071$ ) or the CZP 400mg Q4W group ( $p=0.688$ ). For this analysis, scores for subjects who withdrew for any reason, or subjects with missing week 24 measurement, or placebo subjects who used escape medication were linearly extrapolated from the last two radiographs before week 24 or the early withdrawal or before receiving CZP. Missing baseline mTSS measurements were imputed with the minimum value observed, 0. If a subject was missing at least two measurements including week 24, then the missing week 24 score was imputed with the maximum value observed in this study, 356.5. This value, the largest observed mTSS, originated with a single CZP 400mg Q4W subject. The applicant stated that SAP-defined imputation rules led to physiologically implausible changes in mTSS (mean change of 11.52 in the CZP 200mg Q2W group, 25.05 in the CZP 400mg Q4W group and 28.92 in the placebo group).

A comparison of published structural damage progression data in placebo and active treatment groups across clinical studies for anti-TNF $\alpha$ s revealed that the expected values for change from Baseline in mTSS are orders of magnitude (by a factor of up to 100) lower than the implausibly high values observed in PsA001 when the SAP-defined imputation rules were applied. Therefore, the SAP-defined analyses are not reflective of clinical reality, and to appropriately evaluate the PsA001, different post-hoc imputation rules were applied along with a specified window between radiographs.

In addition, this analysis may be confounded by the fact that more than 40% of placebo subjects escaped and no CZP subjects escaped at week 16 (although 10% of the CZP subjects met escape criteria) (section 3.2.3). Escaped placebo subjects are being included in this analysis primarily through linear extrapolation of their pre-week 16 measurements. It is difficult to determine whether this inequitable need for imputation of missing data would bias the treatment group comparisons in favor of the CZP groups or placebo in the presence of the linear extrapolation methods.

In summary, this reviewer is in agreement with the sponsor that the results of the pre-specified analysis of the change from baseline to week 24 in mTSS shown in Table 10 are not reliable and therefore not informative.

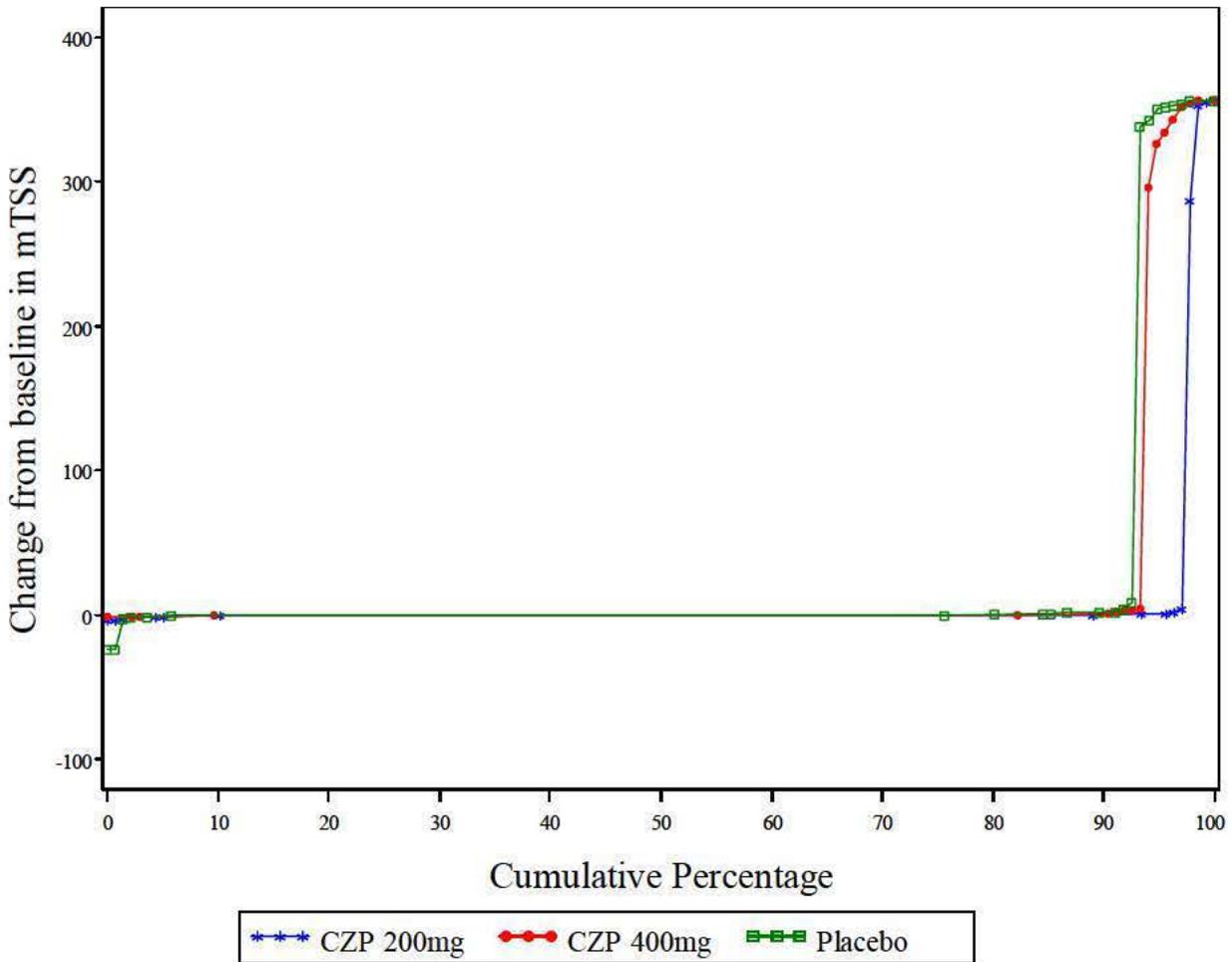
**Table 10 Primary Efficacy Analysis: Change from Baseline in mTSS at Week 24 (RS, Not Utilizing Placebo Escaped Data)**

	Placebo*	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W +400mg Q4W
	N=136	N=138	N=135	N=273
<b>Mean change from baseline (SE)</b>	28.9 (7.7)	11.5 (7.6)	25.1 (7.9)	18.3 (6.1)
<b>Difference between treatment groups (p-value)</b>		-17.4 (0.071)	-3.9 (0.688)	-10.6 (0.203)

Source: Cimzia/Active Psoriatic Arthritis PsA001 Double-Blind-Protocol Number PsA001 Table 4.9.1, page 425

\* For the entire placebo group, linear extrapolations are used for subjects escaping to CZP.

For completeness, the cumulative probability plot for the change from baseline in mTSS score at week 24 while employing the pre-specified imputation methods is provided in Figure 1; however, for the same reasons as previously described, analyses or summaries of mTSS based data resulting from the pre-specified missing data imputation plan are not considered by this reviewer to be reliable. Note that the extreme observations (at a change from baseline of 356.5) were, for all but one subject, imputed not observed values.



**Figure 1 Cumulative Probability Plot for Change from Baseline in mTSS at Week 24 using the SAP-predefined analysis (RS, Not Utilizing Placebo Escaped Data, with SAP pre-specified imputation)**

The following analyses were defined post-hoc by the FDA as alternative (not sensitivity) analyses to replace those pre-specified for the mTSS endpoint since in this reviewer’s opinion; results of the pre-specified analyses were unreliable and uninformative. Two post-hoc FDA analyses will be presented. Both FDA post-hoc analyses exclude subjects with less than two available radiographs with the predefined no minimal time interval between two radiographic measurements since methods for imputing data for these subjects were not obvious post-hoc and would be open to criticism. Subjects with two available and one missing radiograph were included in the analysis and the missing observation was imputed using linear extrapolation. The use of linear extrapolation for imputation of mTSS has been pre-specified and used in several recent similar regulatory programs and is generally thought to be acceptable. Subjects with three available radiographs were included using the observed data.

In the first FDA post-hoc analysis, placebo subjects who escaped are included using their observed data despite their escape. Therefore the proportions of subjects excluded from the analysis as a result of having fewer than two radiographs were fairly small (i.e., 8%, 12%, and 13% in the CZP 200 mg Q2W, CZP 400mg Q4W, and placebo groups respectively). In addition,

the 18 (13%) CZP 200 mg Q2W subjects and 21 (16%) CZP 400 mg Q4W subjects who met the early escape criteria but who did not escape due to the protocol defined escape rules requiring that only placebo subjects could escape are included in this analysis using their observed data. That is these CZP patients who would have been eligible for escape but did not escape are included in the same manner in this analysis as those placebo patients who escaped. The results of this analysis are shown in Table 11. Since placebo subjects who escaped at week 16 were to receive CZP, the inclusion of this observed data would likely cause the placebo group to look artificially similar to each of the CZP groups and therefore, the mTSS analysis at week 24 would remain valid in the presence of demonstration of a positive treatment effect for CZP.

In the second FDA post-hoc analysis, placebo subjects who escaped at week 16 are considered missing and therefore the proportions of subjects excluded from the analysis as a result of having less than two radiographs available were larger (i.e., 8%, 12%, and 19% in the CZP 200 mg Q2W, CZP 400mg Q4W, and placebo groups respectively). For this reason the first FDA post-hoc analysis is likely to be more reliable than the second. Table 12 shows the results of the second FDA post-hoc analysis.

The results from the FDA post-hoc analyses did not concur with the results from the predefined analysis. For both analyses, the mean change from baseline was numerically smaller in both the CZP 200mg Q2W group and the CZP 400mg Q4W groups than placebo, meaning there was less progression of radiographic changes in these two treatment groups compared to the placebo group. The difference in the mean change from baseline in mTSS at week 24 was -0.27 for the CZP 200mg Q2W group not utilizing the placebo escaped CZP data and -0.21 for CZP 200mg Q2W utilizing the placebo escaped CZP data. These differences were considered statistically significant in either analysis (p=0.02 and p=0.008 in the first and second FDA post-hoc analysis, respectively). The differences between the CZP 400mg Q4W group and placebo were numerically but not statistically significantly in favor of the CZP group (p =0.3 and p=0.1 in the first and second FDA post-hoc analysis, respectively).

**Table 11 Reviewer Primary Efficacy Analysis: Change from Baseline in mTSS at Week 24, Exclusion of Subjects with <2 Available Radiographs (RS, Utilizing Placebo Escaped Data)**

	Placebo*	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W +400mg Q4W
	N=136	N=138	N=135	N=273
<b>Sample size</b>	n=123	n=130	n=123	n=253
<b>Mean change from baseline (SE)</b>	0.18 (0.07)	-0.02 (0.07)	0.09 (0.07)	0.03 (0.05)
<b>Difference between treatment groups (p-value)</b>		-0.21 (0.0170)	-0.10 (0.2612)	-0.15 (0.0421)

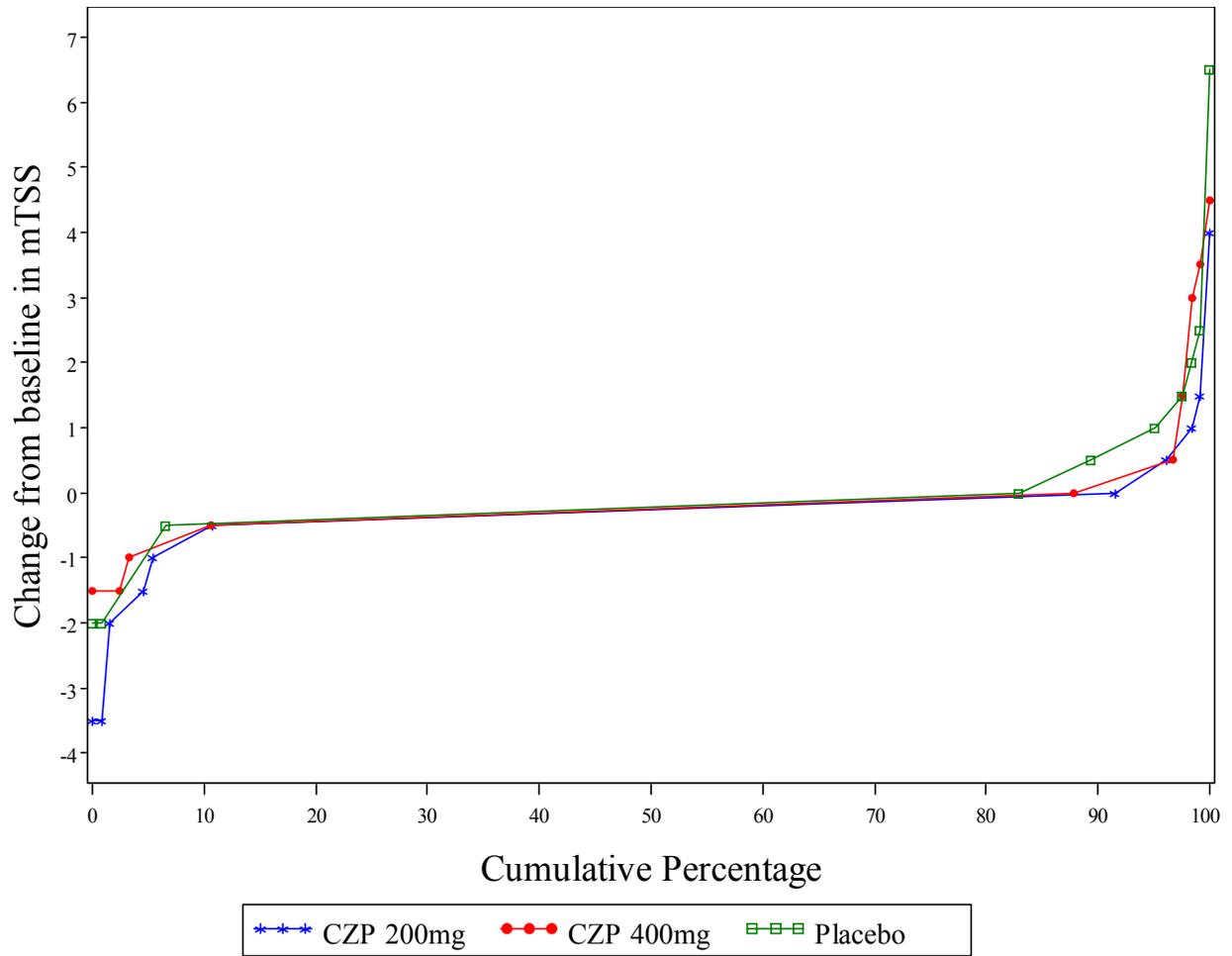
\* For the subjects switching from PBO to CZP their CZP data are utilized for calculation.

**Table 12 Reviewer Primary Efficacy Sensitivity Analysis: Change from Baseline in mTSS at Week 24, Exclusion of Subjects with <2 Available Radiographs (RS, Not Utilizing Placebo Escaped Data)**

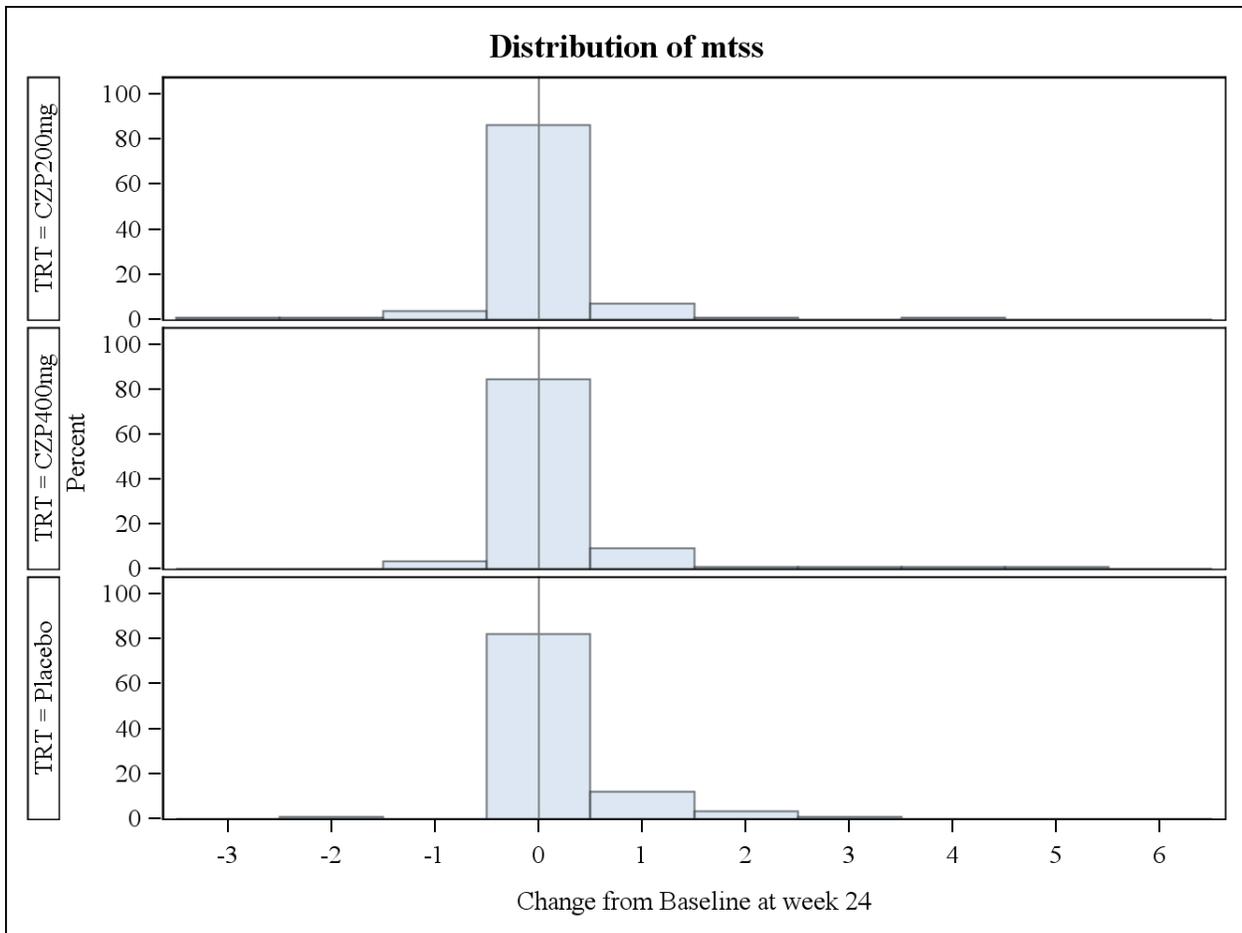
	Placebo*	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W +400mg Q4W
	N=136	N=138	N=135	N=273
<b>Sample size</b>	n=117	n=130	n=123	n=253
<b>Mean change from baseline (SE)</b>	0.27 (0.08)	-0.001 (0.08)	0.11 (0.08)	0.05 (0.06)
<b>Difference between treatment groups (p-value)</b>		-0.27 (0.0079)	-0.16 (0.1220)	-0.21 (0.0156)

\* For the entire placebo group, linear extrapolations are used for subjects escaping to CZP.

The cumulative probability plot for the first FDA post-hoc analysis for the change from baseline in mTSS score at week 24 is shown in Figure 2 and the histogram is shown in Figure 3. Similar to the above figures, a difference between treatment groups is evident as the proportions of subjects in the CZP 200mg Q2W group have a smaller change from baseline than those of placebo subjects. The CZP 400mg Q4W group is slightly more similar to the placebo group. Both figures show that with the exclusion of subjects with less than 2 available radiographs the change from baseline has decreased compared to the pre-defined analysis and imputation rules.

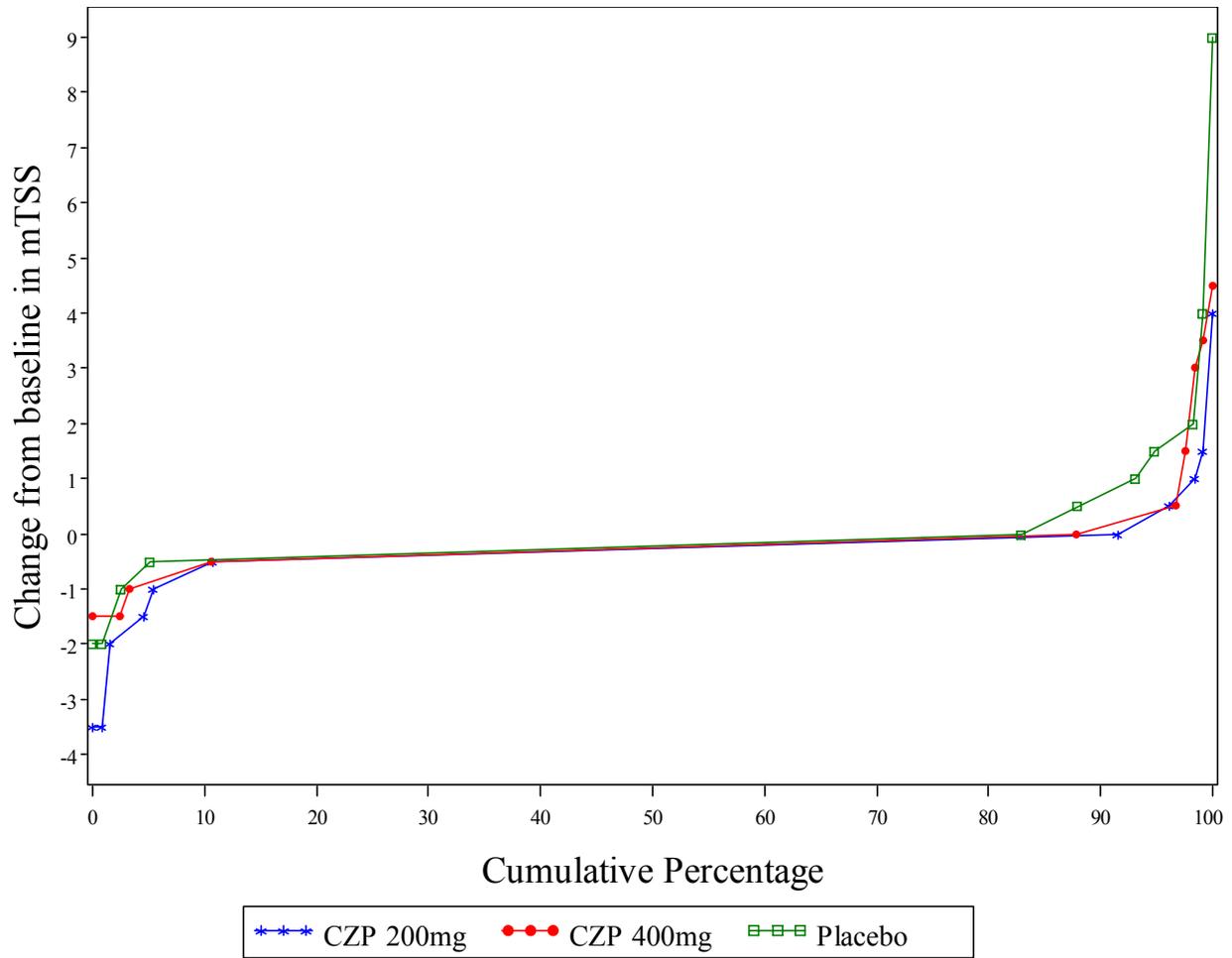


**Figure 2 Cumulative Probability Plot for Change from Baseline in mTSS at Week 24 Excluding Subjects with Less Than 2 Available Radiographs (RS, Utilizing Placebo Escaped Data)**

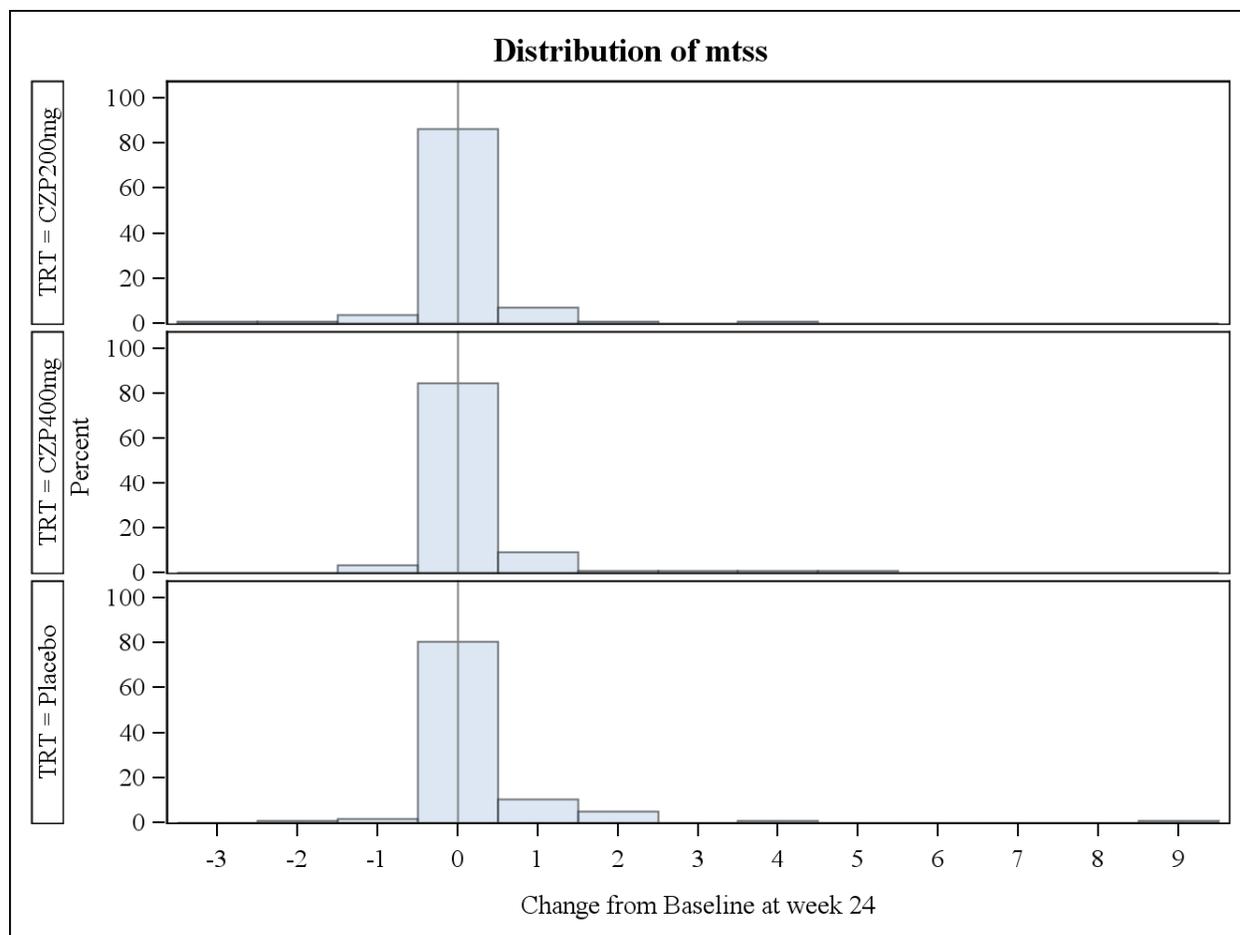


**Figure 3 Histogram for Change from Baseline in mTSS at Week 24 Excluding Subjects with Less Than 2 Available Radiographs (RS, Utilizing Placebo Escaped Data)**

The cumulative probability plot for the second FDA post-hoc analysis for the change from baseline in mTSS score at week is shown in Figure 4. A difference between treatment groups is evident as the proportions of subjects in the CZP 200mg Q2W group have a smaller change from baseline than those of placebo subjects. The CZP 400mg Q4W group is slightly more similar to the placebo group. The corresponding histogram for the change from baseline in mTSS score at week 24 is shown in Figure 5. Both figures show that with the exclusion of subjects with less than 2 available radiographs the change from baseline has decreased compared to the pre-defined analysis and imputation rules.



**Figure 4 Cumulative Probability Plot for Change from Baseline in mTSS at Week 24 Excluding Subjects with Less Than 2 Available Radiographs (RS, Not Utilizing Placebo Escaped Data)**



**Figure 5 Histogram of the Change from Baseline in mTSS at Week 24 Excluding Subjects with Less Than 2 Available Radiographs (RS, Not Utilizing Placebo Escaped Data)**

A FDA post-hoc analysis was also conducted of the mTSS response at week 24 as a supportive analysis. Patients who withdrew early from the study for any reason or placebo subjects who escaped to CZP were considered non-responders from the time they withdrew or when escaped therapy was initiated. Patients with missing mTSS values at a visit were considered non-responders for that particular visit. The results of the responder analysis are shown in Table 13. The proportion of subjects achieving an mTSS response at week 24 was statistically significantly higher in both the CZP 200mg Q2W and the CZP 400mg Q4W groups than the placebo group. The proportion of subjects achieving an mTSS response at week 24 was numerically higher in the CZP 200mg Q2W group compared to the CZP 400mg Q4W group. This analysis supports that the CZP 200mg Q2W dose is effective over placebo.

**Table 13 Reviewer Analysis: mTSS Responders at Week 24**

	<b>Placebo</b>	<b>CZP 200mg Q2W</b>	<b>CZP 400mg Q4W</b>
	<b>N=136</b>	<b>N=138</b>	<b>N=135</b>
<b>Non-progressors (%)</b>	47 (35%)	115 (83%)	103 (76%)
<b>Difference between treatment groups, % (95% CI)</b>		50 (39, 60)	42 (32, 52)
<b>p-value</b>		<0.0001	<0.0001

Since the by-treatment group comparisons for first primary efficacy endpoint, the other major secondary efficacy endpoints and the second primary efficacy endpoint (using the reviewer's analysis) were statistically significant and according to the pre-specified multiplicity plan, inferential statistical analysis may continue to the last major response secondary efficacy endpoint, PASI at week 24 for CZP 200mg Q2W and 400mg Q4W combined. The PASI looks at subjects that have psoriasis covering at least 3% of their body surface. As previously described, this review places more emphasis on the results from the individual groups rather than the results from the CZP combined groups.

The pre-specified statistical analysis of PASI75 response at week 24 is shown in Table 14. The proportion of subjects achieving PASI75 response at week 24 was statistically significantly higher in both the CZP 200mg Q2W (62%) and CZP 400mg Q4W (61%) groups than the placebo group (15%). The difference between the CZP 200mg Q2W group and the placebo group was 47% ( $p < 0.001$ ). The difference between the CZP 400mg Q4W group and the placebo group was 45% ( $p < 0.001$ ). For this analysis, any subject who withdrew from the study for any reason or placebo subjects who escaped to CZP were considered non-responders from the time that they dropped out or when escape medication was initiated.

**Table 14 PASI75 Response at Week 24 for Subjects with at Least 3% Psoriasis BSA at Baseline (RS, with Imputation)**

	<b>Placebo</b>	<b>CZP 200mg Q2W</b>	<b>CZP 400mg Q4W</b>	<b>CZP 200mg Q2W + CZP 400mg Q4W</b>
<b>Week 24</b>	<b>N=86</b>	<b>N=90</b>	<b>N=76</b>	<b>N=166</b>
<b>Responders (%)</b>	13 (15%)	56 (62%)	46 (61%)	102 (61%)
<b>Difference between the treatment groups (p-value)</b>		47% (<0.001)	45% (<0.001)	46% (p<0.001)

Source: Clinical Study Report-Protocol Number PsA001 Table 8-11, page 147.

### 3.3 Evaluation of Safety

Safety evaluations for this submission will be evaluated by the Medical Reviewer. Please refer to her review for more information regarding the safety findings.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

Subgroup analysis on the primary efficacy endpoints, ACR20 response at week 12 and change from baseline in mTSS at week 24, by region, gender, age and race are shown in Table 15 and Table 16, respectively. The subgroup analyses were performed using the RS population.

For ACR20 response at week 12, subjects <45 years of age in the CZP 400mg Q4W group did not show a significant difference from placebo. This may be due to small sample size in this subgroup. Also, there were a very small number of nonwhites in the study as well as Latin American subjects making it hard to detect a difference between the treatment groups for these subgroups. The other results indicate that the treatment effect of CZP over placebo is present and relatively consistent across these subgroups.

**Table 15 Subgroup Analysis of ACR20 Response at Week 12 (Randomized Set)**

	<b>Placebo</b> <b>N=136</b>	<b>CZP 200mg</b> <b>Q2W</b> <b>N=138</b>	<b>CZP 400mg</b> <b>Q4W</b> <b>N=135</b>
<b>Age</b>			
<45 years, n/N (%)	18/56 (32)	38/55 (69)	25/52 (48)
Diff to Placebo, % p-value		37 (<0.001)	16 (0.092)
≥45 years, n/N (%)	15/80 (19)	42/83 (51)	45/83 (54)
Diff to Placebo, % p-value		32 (<0.001)	36 (<0.001)
<b>Gender</b>			
<b>Female</b> , n/N (%)	18/79 (23)	38/74 (51)	30/73 (41)
Diff to Placebo, % p-value		29 (<0.001)	18 (0.015)
<b>Male</b> , n/N (%)	15/57 (26)	42/64 (66)	40/62 (65)
Diff to Placebo, % p-value		39 (<0.001)	38 (<0.001)
<b>Race</b>			
<b>Nonwhite</b> , n/N (%)	1/4 (25)	2/3 (67)	2/2 (100)
Diff to Placebo, % p-value		42 (0.314)	75 (NC)
<b>White</b> , n/N (%)	32/132 (24)	78/135 (58)	38/133 (51)
Diff to Placebo, % p-value		34 (<0.001)	27 (<0.001)
<b>Region</b>			
<b>North America</b> , n/N (%)	7/32 (22)	16/31 (52)	22/35 (63)
Diff to Placebo, % p-value		30 (0.013)	41 (<0.001)
<b>Latin America</b> , n/N (%)	12/19 (63)	18/21 (86)	13/20 (65)
Diff to Placebo, % p-value		23 (0.106)	2 (0.906)
<b>West Europe</b> , n/N (%)	6/22 (27)	11/17 (65)	10/16 (63)
Diff to Placebo, % p-value		37 0.019	35 (0.031)
<b>East Europe</b> , n/N (%)	8/63 (13)	35/69 (51)	25/64 (39)
Diff to Placebo, % p-value		38 (<0.001)	26 (<0.001)

Source: Clinical Study Report-Protocol Number PsA001 Table 8-32, page 193-194.

NC: not calculated

For change from baseline in mTSS at week 24, a conclusion could not be drawn for non-whites due to a very small number of subjects in this subgroup. Subjects who were male or white had greater mean differences in the 200mg Q2W group compared to placebo, meaning they had less progression of radiographic changes.

**Table 16 Subgroup Analysis of Change from Baseline in mTSS at Week 24 (Randomized Set, Exclusion of Subjects with Less than 2 Available Radiographs, FDA post-hoc defined)**

	<b>Placebo</b> N=123	<b>CZP 200mg</b> <b>Q2W</b> N=130	<b>CZP 400mg</b> <b>Q4W</b> N=123
<b>Age</b>			
<b>&lt;45 years, n</b>	50	53	48
Mean (SE)	0.18 (0.11)	-0.03 (0.10)	0.12 (0.11)
Diff to Placebo, Mean (SE), p-value		-0.21 (0.13) (0.1067)	-0.05 (0.13) (0.6844)
<b>≥45 years, n</b>	73	77	75
Mean (SE)	0.21 (0.10)	-0.01 (0.09)	0.06 (0.09)
Diff to Placebo, Mean (SE), p-value		-0.22 (0.12) (0.0599)	-0.16 (0.12) (0.1936)
<b>Gender</b>			
<b>Female, n</b>	73	69	66
Mean (SE)		0.01 (0.09)	0.13 (0.10)
Diff to Placebo, Mean (SE), p-value		-0.11 (0.12) (0.3521)	0.01 (0.12) (0.9544)
<b>Male, n</b>	50	61	57
Mean (SE)		-0.04 (0.10)	0.04 (0.10)
Diff to Placebo, Mean (SE), p-value		-0.29 (0.13) (0.0304)	-0.20 (0.13) (0.1238)
<b>Race</b>			
<b>Nonwhite, n</b>	3	1	1
Mean (SE)	-	-	-
Diff to Placebo, Mean (SE), p-value		-	-
<b>White, n</b>	120	129	122
Mean (SE)	0.19 (0.07)	-0.02 (0.07)	0.09 (0.07)
Diff to Placebo, Mean (SE), p-value		-0.21 (0.09) (0.0155)	-0.10 (0.09) (0.2447)
<b>Region</b>			
<b>North America, n</b>	29	29	34
Mean (SE)	-0.02 (0.10)	-0.13 (0.10)	0.02 (0.09)
Diff to Placebo, Mean (SE), p-value		-0.11 (0.14) (0.4301)	0.04 (0.14) (0.7696)
<b>Latin America, n</b>	16	17	17
Mean (SE)	0.46 (0.24)	0.22 (0.22)	0.26 (0.21)
Diff to Placebo, Mean (SE), p-value		-0.25 (0.26) (0.3493)	-0.20 (0.26) (0.4378)
<b>West Europe, n</b>	19	17	16
Mean (SE)	0.07 (0.10)	-0.16 (0.10)	-0.10 (0.12)
Diff to Placebo, Mean (SE), p-value		-0.22 (0.14) (0.1077)	-0.17 (0.14) (0.2244)
<b>East Europe, n</b>	59	67	56
Mean (SE)	0.41 (0.13)	0.16 (0.12)	0.30 (0.14)
Diff to Placebo, Mean (SE), p-value		-0.25 (0.14) (0.0823)	-0.11 (0.15) (0.4646)

\*Utilizing placebo escaped data

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

During the course of this review, the following statistical issues were identified and resolved. Each issue is further described in the context of the referenced sections.

- Inequitable management of escape for placebo and CZP subjects (sections 3.2.1 and 3.2.2)
- Pooling of CZP dose groups for analysis and specification in the multiplicity plan (sections 3.2.2 and 3.2.4)
- Pre-specified missing data imputation for the second primary efficacy endpoint, mTSS was not ideal and post-hoc analysis proposed by the sponsor was not acceptable (sections 3.2.2 and 3.2.4)

### 5.2 Collective Evidence

Since a single phase 3 study was reviewed in support of this application, no assessment of collective evidence across studies is provided in this review and the reader is referred to section 5.3 for the conclusions and recommendations resulting from the review of study PsA001.

### 5.3 Conclusions and Recommendations

Study PsA001 demonstrates statistically significant affects on the first primary efficacy endpoint, ACR20 at week 12 and for the major secondary efficacy endpoints, HAQ-DI at week 24 and PASI75 at week 24 for the individual CZP 200mg Q2W and CZP 400mg Q4W groups relative to placebo. These conclusions are not sensitive to the methods applied for missing data. The pre-defined analysis for the second primary efficacy endpoint, change from baseline in mTSS at week 24, did not demonstrate statistically significant effects for any of the CZP doses compared to placebo. This was at least partially due to the SAP pre-defined imputation rules put in place by the applicant, which led to an unusually high score being imputed for missing mTSS data. Post-hoc FDA-defined sensitivity analyses were conducted to explore the impact of various assumptions regarding the missing data on the treatment effect. These sensitivity analyses included utilizing and not utilizing data from the placebo escaped subjects. The analyses excluding subjects with less than two available radiographs, whether utilizing the placebo escaped data or not utilizing the placebo escaped data, both demonstrated statistically significant effects on mTSS for CZP 200mg Q2W relative to placebo. The CZP 400 mg Q4W group was not statistically significantly different from placebo; however, the effects did trend in the same direction as the CZP 200mg Q2W group.

No statistically significant differences in the treatment effect in terms of the primary efficacy endpoints across gender, race, age or geographic region categories were identified.

#### 5.4 Labeling Recommendations

The sponsor has proposed text to be inserted in section 14 of the product label to describe the results of study PsA001. This text includes [REDACTED] (b) (4)

[REDACTED] Therefore, from a statistical perspective, these endpoints should not be described in labeling unless description of these endpoints is necessary from a clinical perspective to understand the full context of the treatment effect. [REDACTED] (b) (4)

[REDACTED] We suggest the applicant use the results from the first FDA post-hoc analysis to describe results for mTSS.

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/s/  
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KIYA HAMILTON  
08/28/2013

RUTHANNA C DAVI  
08/28/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125160Origs213**

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

## CLINICAL PHARMACOLOGY REVIEW

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BLA	125160/213
Submission Date:	11/28/2012
Brand Name	Cimzia <sup>®</sup>
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	<ul style="list-style-type: none"><li>• 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</li><li>• Treatment of adults with moderately to severely active rheumatoid arthritis</li></ul>
Approved Dosage Regimen	<b>Crohn's Disease</b> 400 mg initially and at Weeks 2 and 4. If response occurs, follow with 400 mg every four weeks <b>Rheumatoid Arthritis</b> 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 psoriatic arthritis (PsA)
Proposed Dosage Regimen	<b>Psoriatic Arthritis</b> 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 (b) (4)

---

## 1 Recommendation

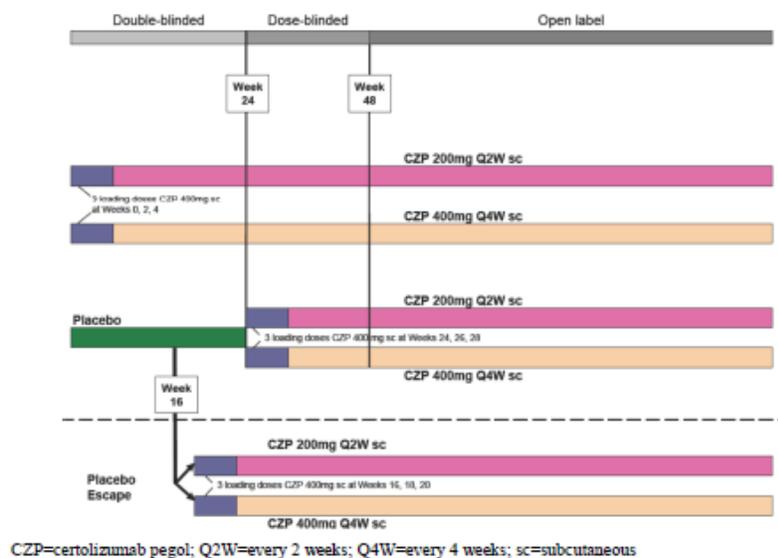
From a Clinical Pharmacology perspective, the application is acceptable.

## 2 Overall clinical pharmacology findings

Out of the five approved tumor necrosis factor alpha (TNF $\alpha$ ) antagonists (infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol), certolizumab is the only one that is not currently registered in the US and Europe for the treatment of PsA. Therefore, the sponsor is applying for the approval of Cimzia for the PsA indication, with the notion that the need remains for additional TNF $\alpha$  antagonists as a therapeutic option for PsA, as lack of response to an initial TNF $\alpha$  antagonist may not preclude the response to another one.

The PsA clinical development program was discussed with the FDA prior to its initiation. This efficacy supplement is supported by a single Phase III (efficacy and safety) study PsA001. 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. PsA001 is a Phase III, multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study to evaluate the efficacy and safety of CZP in adult subjects with active and progressive PsA. As shown in Figure 1, study PsA001 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. Suzette Peng and statistical reviewer Dr. Kiya Hamilton. Refer to their reviews for details.

Figure 1 Study design of PsA001



No clinical pharmacology studies have been included in the submission and no clinical pharmacology related label changes have been proposed by sponsor. In study PsA001, no additional clinical pharmacology information has been collected and there were too few antibody positive subjects to draw meaning conclusion regarding immunogenicity for the indication of PsA.

### **2.1 Summary of the proposed label revisions related to clinical pharmacology**

None.

### **3 Proposed label revisions**

None.

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LIANG ZHAO  
08/22/2013

SATJIT S BRAR  
08/22/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125160Origs213**

**OTHER REVIEW(S)**

**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 15, 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)**

Adewale Adeleye, Pharm.D, MBA  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG) and  
Instructions for Use (IFU)

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: 213

Applicant: UCB, Inc.

## **1 INTRODUCTION**

On November 29, 2012, UCB, Inc. submitted for the Agency's review a Prior Approval Efficacy Supplement (PAS-213) to the Biologics Licensing Application (BLA 125160) for CIMZIA (certolizumab pegol) lyophilized powder or solution for subcutaneous use. The purpose of this submission is to provide for the addition of a new indication for the treatment of adults with active Psoriatic Arthritis.

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 collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology (DPARP) on December 14, 2012 and December 14, 2012, respectively. DPARP requested that DMPP and OPDP review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) 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 November 29, 2012 and received by DMPP on December 14, 2012
- Draft CIMZIA (certolizumab pegol) lyophilized powder or solution for subcutaneous use Prefilled Syringe Instructions for Use (IFU) received on January 16, 2013 and received by DMPP on January 16, 2013
- Draft CIMZIA (certolizumab pegol) lyophilized powder or solution for subcutaneous use Medication Guide (MG) received on November 29, 2012 and received by OPDP on August 08, 2013
- Draft CIMZIA (certolizumab pegol) lyophilized powder or solution for subcutaneous use Prefilled Syringe Instructions for Use (IFU) received on January 16, 2013 and received by OPDP on August 08, 2013
- Draft CIMZIA (certolizumab pegol) lyophilized powder or solution for subcutaneous use Prescribing Information (PI) received on November 29, 2012, revised throughout the review cycle and received by DMPP on August 2, 2013
- Draft CIMZIA (certolizumab pegol) lyophilized powder or solution for subcutaneous use Prescribing Information (PI) received on November 29, 2012, revised throughout the review cycle and received by OPDP on August 08, 2013
- Approved ILARIS (canakinumab) comparator labeling dated May 9, 2013

## **3 REVIEW METHODS**

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG and IFUs, the target reading level is at or below an 8<sup>th</sup> grade level.

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

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU 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 and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our annotated version of the MG and IFU are appended to this memo. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/  
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SHAWNA L HUTCHINS  
08/15/2013

ADEWALE A ADELEYE  
08/15/2013

MELISSA I HULETT  
08/15/2013

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

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

## Memorandum

**Date:** August 15, 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-213 - CIMZIA (certolizumab pegol) Lyophilized  
powder or solution for subcutaneous use (Cimzia)

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Reference is made to DPARP's consult request dated December 14, 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 psoriatic arthritis.

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 entitled, "BLA 125160 S213 2-18-2013 updated PI Clean.doc" that was sent via e-mail from DPARP to OPDP on August 2, 2013. OPDP has no comments at this time on the proposed PI.

Please note that comments on the proposed MG will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

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

36 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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ADEWALE A ADELEYE  
08/15/2013

**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

(b) (4)

- 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.

<b>Table 1: FAERS Search Strategy</b>	
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,<sup>1</sup> 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 reporter<sup>2</sup>.

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.

---

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

<sup>2</sup> 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 (b) (4)

(b) (4) 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 (b) (4)

(b) (4) 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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TERESA S MCMILLAN  
06/17/2013

LUBNA A MERCHANT  
06/17/2013

**Division of Pulmonary, Allergy, and Rheumatology Products**

**REGULATORY PROJECT MANAGER LABELING REVIEW**

**Application:** BLA 125160/213 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:** November 28, 2012

**Receipt Date:** November 29, 2012

**Background and Summary Description:**

This supplemental application proposes an indication for the treatment of active psoriatic arthritis in adults. 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**

A side-by-side comparison of the revised labeling submitted on February 18, 2013, to the last approved labeling for S-189 dated November 15, 2012, was conducted. The sponsor submitted the updated content of labeling February 18, 2013, based on the comments provided in the Filing Communication letter dated January 25, 2013. The labeling format issues identified in the Filing Communication letter were corrected. Below are the proposed revisions submitted by the UCB, Inc.

**Highlights Section (HL)**

- The heading for the Boxed Warning has been changed from [REDACTED] (b) (4) to WARNING: SERIOUS INFECTIONS AND MALIGNANCY.
- The following were added to the Recent Major Changes:
  - Indications and Usage (1.3) xx/2013
  - Dosage and Administration (2.3; 2.7) xx/2013
  - Warnings and Precautions, [REDACTED] (b) (4) (5.2) 11/2012
  - Warnings and Precautions, [REDACTED] (b) (4) (5.5) 10/2012
  - [REDACTED] (b) (4) [REDACTED] (b) (4)
- The following was added to Indications and Usage:
  - Treatment of adult patients with active psoriatic arthritis. (1.3)

- The following was added to Dosage and Administration:  
Psoriatic Arthritis (2.3)
  - 400 mg (b)(4) initially and at week 2 and 4, followed by 200 mg every other week (b)(4)

**Full Prescribing Information (FPI)**

- The following was added to Section 1, Indications and Usage:
  - 1.3 Psoriatic Arthritis  
CIMZIA is indicated for the treatment of adult patients with active psoriatic arthritis (PsA).
- The following were added to Section 2, Dosage and Administration:
  - 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 (b)(4)
  - 2.7 Concomitant Medications  
In the psoriatic arthritis clinical study, oral corticosteroids, DMARDs (methotrexate, leflunomide, sulfasalazine, (b)(4)) and NSAIDs were permitted as concomitant therapy.
- The following was added to Section 6, Adverse Reactions:
  - 6.1 Clinical Trials Experience  
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.
- Subsection 14.3 Psoriatic Arthritis 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	April 22, 2013
Regulatory Project Manager	Date

Ladan Jafari	April 22, 2013
Chief, Project Management Staff	Date

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PHUONG N TON  
04/22/2013

LADAN JAFARI  
04/23/2013



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation III  
Division of Dermatology and Dental Products  
Silver Spring MD 20993

Tel: 301 796-2110  
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## MEMORANDUM

Date: February 1, 2013

From: David Kettl, MD, Clinical Team Leader, DDDP

Through: Susan Walker, MD, Division Director, DDDP

To: Badrul Chowdhury, MD, Division Director, DPARP

Cc: Barbara Gould, CPMS, DDDP  
Rachel Attinello, RPM, DDDP  
Suzette Peng, MD, DPARP  
Sarah Yim, MD, DPARP  
Nina Ton, PharmD, RPM, DPARP

Re: DDDP Consult #1485: BLA 125160, Supplement S-213  
Cimzia (certolizumab pegol) (b) (4)

### Material Reviewed:

Proposed labeling for Cimzia related to newly proposed indication for psoriatic arthritis.

### Background:

DPARP Request: "DPARP received an efficacy supplement, S-213 dated November 29, 2012, for psoriatic arthritis indication. The PDUFA goal date for S-213 is September 29, 2013. This supplement contains (b) (4)

We would appreciate your input on the clinical meaningfulness, strengths and weaknesses of the (b) (4) and (b) (4)

### Review:

Cimzia (certolizumab pegol) is a tumor necrosis factor (TNF) blocker marketed for subcutaneous use in a lyophilized powder or solution. Cimzia was initially licensed (#1736) in the US on April 22, 2008, and was initially indicated for reducing the signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

It currently (2/1/2013) 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, and

Treatment of adults with moderately to severely active rheumatoid arthritis.

The applicant proposes a new indication of treatment of psoriatic arthritis in the current efficacy supplement. DPARP consulted DDDP regarding the (b) (4)

(b) (4)

(b) (4)

The applicant proposes the following (b) (4) which will describe (b) (4) related to psoriatic arthritis:

(b) (4)

DDDP Comments:

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

**Conclusions:**

While the final decision [REDACTED] (b) (4) for psoriatic arthritis resides in DPARP, DDDP recommends that the [REDACTED] (b) (4)

[REDACTED] (b) (4) and can contact DDDP for further information.

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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.**  
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/s/  
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DAVID L KETTL  
02/12/2013

SUSAN J WALKER  
02/12/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125160Origs213**

**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 $\alpha$ ), 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  $\leq 0$ . 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 (b) (4) of the Cimzia label.***

(b) (4)

(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, [REDACTED] (b) (4) [REDACTED] 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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## 2.11. 120-Day Safety Update for Both Indications

***Question 11:*** *Due to the size and supportive nature of the RA safety pooling database, UCB proposes a targeted approach that would refresh the PsA001 and AS001 safety in the 120-Day Safety Update as follows:*

- *Study medication exposure.*
- *Subject accountability.*
- *Adverse events (AEs), AE by SOC, SAEs, PTAEs, deaths, markedly abnormal laboratory values, and anti-CZP antibodies.*
- *Narratives for subjects with SAEs, PTAEs, and deaths.*

*Does the Agency agree with this proposal?*

*FDA Response to Question 11:* *Your proposal is generally acceptable.*

### 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 UBC on 09 May 2011, and all subsequent notifications contained the correct randomization date at Week 0.*
- *The potential for unblinding did not occur until Week 16. However, in order to avoid changes to the Week 12 paper CRF pages and any potential impact on the primary variables, the site monitors were instructed to prioritize the collection of the Week 12 CRF pages. The reason for this request was not conveyed to the monitors to avoid potential bias.*

*UCB realizes the integrity of the studies will be a review issue; however, does the Agency concur that these corrective actions are adequate?*

*FDA Response to Question 12:* *We cannot comment on the adequacy of these corrective actions until the data are reviewed.*

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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](mailto: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.

Meeting Minutes  
Type B

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.

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PHILANTHA M BOWEN  
08/24/2012