AUSTRALIAN PRODUCT INFORMATION

CIMZIA® (CERTOLIZUMAB PEGOL) 200 MG/ML INJECTION

1 NAME OF THE MEDICINE

Certolizumab pegol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cimzia injection contains 200 mg certolizumab pegol per mL.

Certolizumab pegol is a recombinant, humanised antibody Fab' fragment that is expressed in an *Escherichia coli* bacterial expression system, subsequently purified and conjugated to polyethylene glycol (PEG).

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

200 mg/mL Injection in a single-use pre-filled syringe or pre-filled pen (AutoClicks®)
Cimzia® injection is a sterile clear to opalescent solution that is colourless to yellow, essentially free of visible particles.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Rheumatoid arthritis
Cimzia is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients.

- Combined with MTX in case of either an inadequate response or intolerance to previous therapy with one or more disease modifying antirheumatic drugs (DMARDs) or

- As monotherapy in case of a contraindication or intolerance to MTX (see Section 4.2 Dose and Method of Administration).

Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX.

Cimzia in combination with MTX is indicated for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX or other DMARDs.

Psoriatic arthritis
Cimzia is indicated for the treatment of adult patients with active psoriatic arthritis where response to previous disease modifying antirheumatic drug therapy (DMARDs) has been inadequate. Cimzia has been shown to improve physical function.

Ankylosing spondylitis
Cimzia is indicated for the treatment of adult patients with active, ankylosing spondylitis who have been intolerant to or have had inadequate response to at least one nonsteroidal anti-inflammatory drug (NSAID).

Non-radiographic Axial Spondyloarthritis
Cimzia is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C reactive protein (CRP) and /or magnetic resonance imaging (MRI) change, who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis
Cimzia is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Cimzia treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis and plaque psoriasis. After proper training in injection technique, patients may self inject with Cimzia if their physician determines that it is appropriate and with medical follow-up as necessary.

Loading dose
The recommended loading dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) initially (Week 0) and at Weeks 2 and 4.

Maintenance dose
Rheumatoid arthritis
After the loading dose, the recommended maintenance dose of Cimzia for adult patients with rheumatoid arthritis is 200 mg every 2 weeks via subcutaneous injection. Alternatively, Cimzia 400 mg every 4 weeks has been shown to be safe and effective.

No additional benefit has been observed with doses above a total dose of 400 mg/monthly (see Section 5.1 Pharmacodynamic Properties, Clinical trials).

Psoriatic arthritis
After the loading dose, the recommended maintenance dose of Cimzia for adult patients with psoriatic arthritis is 200 mg every 2 weeks. Alternatively, Cimzia 400 mg every 4 weeks can be considered.

Ankylosing spondylitis
After the loading dose, the recommended dose of Cimzia for adult patients with ankylosing spondylitis is 200 mg every 2 weeks or 400 mg every 4 weeks. After at least 1 year of treatment with Cimzia, in patients with sustained remission, a reduced maintenance dose of 200 mg every 4 weeks may be considered (see Section 5.1 Pharmacodynamic Properties, Clinical trials).

Non-radiographic Axial Spondyloarthritis
After the loading dose, the recommended dose of Cimzia for adult patients with non-radiographic axial spondyloarthritis is 200 mg every 2 weeks or 400 mg every 4 weeks. After at least 1 year of

treatment with Cimzia, in patients with sustained remission, a reduced maintenance dose of 200 mg every 4 weeks may be considered (see Section 5.1 Pharmacodynamic Properties, Clinical trials).

For the above indications, available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continuation of therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment.

Plaque psoriasis
After the loading dose, the maintenance dose of Cimzia for adult patients with plaque psoriasis is 200 mg every 2 weeks or 400 mg every 2 weeks. A dose of 400 mg every 2 weeks may be specifically considered in patients with an insufficient response to 200 mg every 2 weeks or in patients with a body weight of 90 kg and above (see Section 5.1 Pharmacodynamic Properties, Clinical trials).

Continuation of therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 16 weeks of treatment. In some patients, a clinical response is only achieved after 16 weeks of treatment (see section 5.2 Pharmacokinetic Properties, Pharmacokinetic/pharmacodynamic relationship).

Children and adolescents
There is no experience in children or adolescents below 18 years of age.

Elderly
No dose adjustment is required. Population pharmacokinetic analyses showed no effect of age.

Renal impairment
There are insufficient data to provide dosing recommendations in moderate and severe renal impairment (see Section 5.2 Pharmacokinetic Properties).

Hepatic impairment
Specific clinical studies have not been performed to assess the effect of hepatic impairment on the pharmacokinetics of Cimzia.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see Section 4.4 Special Warnings and Precautions for Use).

Active tuberculosis or other severe infections such as sepsis or opportunistic infections (see Section 4.4 Special Warnings and Precautions for Use).

Concurrent administration of Cimzia and anakinra (an interleukin-1 receptor antagonist) is contraindicated.

Moderate to severe heart failure (NYHA classes III/IV) (see Section 4.4 Special Warnings and Precautions for Use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Immunosuppression
Since Tumour Necrosis Factor (TNF) mediates inflammation and modulates cellular immune responses, the possibility exists for TNF blocking agents, including Cimzia, to affect host defences

against infections and malignancies. Patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis may not manifest typical symptoms of infection, including fever, due to their disease and concomitant medications. Therefore, early detection of any infection is critical to minimise delays in diagnosis and initiation of treatment.

Infections
Patients must be monitored closely for signs and symptoms of infections including tuberculosis before, during and after treatment with Cimzia, taking into account the 14 day half-life of the product. Because the elimination of certolizumab pegol may take up to 5 months, monitoring should be considered throughout this period. Treatment with Cimzia should not be initiated in patients with a clinically important active infection, including chronic or localised infections, until the infection is controlled (see Section 4.3 Contraindications).

Patients who develop a new infection while undergoing treatment with Cimzia should be monitored closely. Administration of Cimzia should be discontinued if a patient develops a new serious infection until the infection is controlled. Physicians should exercise caution when considering the use of Cimzia in patients with a history of recurring, opportunistic infection, chronic infections or with underlying conditions which may predispose patients to infections.

Serious infections due to bacterial, mycobacterial, invasive fungal, viral and/or parasitic pathogens, sepsis, tuberculosis (including miliary, disseminated and extrapulmonary disease) and opportunistic infections have been reported in patients receiving TNF blocking agents including Cimzia. Some of these events have been fatal. Among opportunistic infections, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, nocardiosis, listeriosis, and pneumocystosis were the most frequently reported. Many of the serious infections reported have occurred in patients on concomitant immunosuppressive therapy that, in addition to their rheumatoid arthritis, could predispose them to infections (see Section 4.8 Adverse Effects (Undesirable Effects)).

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.

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.

Before initiation of therapy with Cimzia, all patients must be evaluated for both active and inactive (latent) tuberculosis infection. This evaluation should include a detailed medical history for patients with a personal history of tuberculosis, with possible previous exposure to others with active tuberculosis, and with previous and/or current use of immunosuppressive therapy. Appropriate screening tests, e.g. tuberculin skin test and chest X-ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the patient's alert card. Prescribers are reminded of the risk of false negative tuberculin skin test

results, especially in patients who are severely ill or immunocompromised. Biological tests for tuberculosis screening should be considered before starting Cimzia treatment if there is any potential latent tuberculosis infection, regardless of BCG vaccination.

If active tuberculosis is diagnosed, Cimzia therapy must not be initiated and must be discontinued (see Section 4.3 Contraindications). If latent tuberculosis is diagnosed, appropriate antituberculosis prophylaxis must be started before initiating treatment with Cimzia and in accordance with local recommendations. In this situation, the benefit/risk balance of therapy with Cimzia should be very carefully considered. Patients should be instructed to seek medical advice if signs/symptoms (e.g. persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after therapy with Cimzia (see Section 4.8 Adverse Effects (Undesirable Effects)). Despite previous or concomitant prophylactic treatment for tuberculosis, cases of active tuberculosis have occurred in patients treated with TNF-antagonists including Cimzia.

Hepatitis B virus (HBV) reactivation
Reactivation of hepatitis B occurred in patients receiving a TNF-antagonist including Cimzia, who are chronic carriers of this virus (i.e. surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF-antagonist therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation.

Patients should be tested 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 TNF-antagonist therapy, in conjunction with antiviral therapy, to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF-antagonists 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, Cimzia should be discontinued and effective antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF-antagonist therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of Cimzia therapy in this situation and monitor patients closely.

Malignancies and lymphoproliferative disorders
In clinical studies with Cimzia and other TNF-antagonist agents, more cases of lymphoma and other malignancies have been observed among patients receiving TNF-antagonists than in control patients receiving placebo. However, the occurrence was uncommon or rare, and the observation period for patients on placebo was shorter than for patients receiving TNF-antagonist therapy. Furthermore, the background lymphoma risk in rheumatoid arthritis patients complicates the risk estimation. A possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-antagonist agents (initiation of therapy ≤ 18 years of age) of which Cimzia is a member (see Paediatric use). 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 postmarketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma that has a very aggressive disease course and is usually fatal, have been reported in patients treated with TNF-antagonists. The majority of the reported TNF-antagonist cases occurred in adolescent and young adult males with Crohn's disease or ulcerative colitis. Almost all of these patients had received treatment with the immunosuppressants azathioprine and/or 6-mercaptopurine concomitantly with a TNF-antagonist prior to diagnosis.

In the Cimzia RA clinical trials (placebo controlled and open label) a total of 5 cases of lymphoma were observed among 4049 patients. 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-antagonists and may not predict the rates observed when Cimzia is used in a broader patient population. The potential role of TNF-antagonist therapy in the development of malignancies in adults is not known.

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

No studies have been conducted that include patients with a history of malignancy, or that continue treatment in patients who develop malignancy, while receiving Cimzia. Thus, particular caution should be exercised in considering Cimzia treatment of these patients. Patients treated with Cimzia should be monitored for symptoms of malignancy and be instructed to inform their physician of any changes to their general health (see Section 4.8 Adverse Effects (Undesirable Effects)).

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

Chronic obstructive pulmonary disease (COPD)
In an exploratory clinical trial evaluating the use of another TNF-antagonist, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in active treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking.

Congestive heart failure
In a clinical trial with another TNF-antagonist, worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of congestive heart failure have also been reported in rheumatoid arthritis patients receiving Cimzia. Cimzia should be used with caution in patients with mild heart failure (NYHA class I/II). Cimzia is contraindicated in moderate or

severe heart failure. Treatment with Cimzia must be discontinued in patients who develop new or worsening symptoms of congestive heart failure (see Section 4.8 Adverse Effects (Undesirable Effects)).

Haematologic events
Reports of pancytopenia, including aplastic anaemia, have been rare with TNF-antagonists. Adverse events of the haematologic system, including medically significant cytopenia (e.g. leukopenia, pancytopenia, and thrombocytopenia) have been infrequently reported with Cimzia. 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. All patients should be advised 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. Discontinuation of Cimzia therapy should be considered in patients with confirmed significant haematologic abnormalities.

Neurological events
Use of TNF-antagonists has been associated with rare cases of 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. Prescribers should exercise caution in considering the use of Cimzia in patients with pre-existing or recent onset central nervous system demyelinating disorders. Rare cases of neurological disorders, including seizure disorder, cranial nerve neuritis, peripheral neuropathy and transverse myelitis, have been reported in patients treated with Cimzia.

Hypersensitivity
The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following Cimzia administration to patients: angioedema, dyspnea, hypotension, rash, serum sickness, and urticaria. Some of these reactions occurred after the first administration. 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-antagonist; in these patients caution is needed (see Section 4.8 Adverse Effects (Undesirable Effects)).

Latex sensitivity
The needle shield inside the removable cap of the CIMZIA pre-filled syringe and pre-filled pen (AutoClicks®) contains 7 % of a derivative of natural rubber latex (see Section 6.5 Nature and Contents of Container). The needle shield does not come into direct contact with the patient or injection administrator. Nevertheless, a potential risk of hypersensitivity reactions cannot be completely excluded in latex-sensitive individuals.

Autoimmune processes
Treatment with Cimzia may result in the formation of autoantibodies and, uncommonly, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Cimzia, treatment should be discontinued. Cimzia has not been studied specifically in a lupus population (see Section 4.8 Adverse Effects (Undesirable Effects)).

Vaccinations
No data are available on the response to live vaccinations or the secondary transmission of infection by live vaccines in patients receiving Cimzia. Live or live attenuated vaccines should not be

administered concurrently with Cimzia. Patients treated with Cimzia may receive inactivated vaccines on the basis of data from recently completed clinical trials.

In a placebo controlled clinical trial of patients with rheumatoid arthritis (RA0017), no meaningful difference was detected in antibody response 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 antibodies between Cimzia and placebo treatment groups (see Table 1).

Table 1: Satisfactory humoral response at week 6

	Cimzia % (n/N)	Placebo % (n/N)	Difference in proportion [95 % CI]
Pneumococcal vaccine	54.5% (48/88)	62.5% (55/88)	-0.080 [-0.225; 0.066]
Influenza vaccine	53.5% (46/86)	61.4% (51/83)	-0.080 [-0.229; 0.070]

(Note: A humoral responder is defined as a subject with:
- a ≥2-fold increase at Week 6 from vaccination at Week 2 in ≥3 of 6 pneumococcal antigens 6B, 9V, 14, 18C, 19F, and 23F;
- a ≥4-fold increase at Week 6 from vaccination at Week 2 in ≥2 of 3 influenza antigens H1N1 (nonpandemic), H3N2, and B).

However, patients receiving Cimzia and concomitant methotrexate had a lower humoral response compared with patients receiving Cimzia alone (see Table 2). The clinical significance of this is unknown.

Table 2: Satisfactory humoral response at week 6 per concomitant use of MTX

	Placebo % (n/N)	CIMZIA % (n/N)	Difference in proportion [95 % CI]	Placebo + MTX % (n/N)	CIMZIA + MTX % (n/N)	Difference in proportion [95 % CI]
Pneumococcal vaccine	89.3% (25/28)	80.0% (20/25)	-0.093 [-0.286; 0.100]	50.0% (30/60)	44.4% (28/63)	-0.056 [-0.232; 0.121]
Influenza vaccine	84.6% (22/26)	70.4% (19/27)	-0.142 [-0.368, 0.083]	50.9% (29/57)	45.8% (27/59)	-0.051 [-0.233; 0.131]

Cimzia does not significantly suppress the protective humoral immune response to the pneumococcal polysaccharide vaccine or influenza vaccine.

Concurrent administration of TNF-alpha inhibitor and other biologics
Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) or abatacept and another TNF-antagonist agent, with no added benefit compared to TNF-antagonist therapy alone. Because of the nature of the adverse events seen with the combination of another TNF-antagonist agent with abatacept or anakinra therapy, similar toxicities may also result from the combination of anakinra or abatacept and other TNF-antagonists. Therefore, the use of Cimzia in combination with anakinra or abatacept, or any other biological response modifier, is not recommended.

Surgery
There is limited safety experience with surgical procedures in patients treated with Cimzia. The 14 day half-life of certolizumab pegol should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Cimzia should be closely monitored for infections, and appropriate actions should be taken.

Psoriasis - new onset and exacerbations
Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis and cases of exacerbation of pre-existing psoriasis have been reported with the use of TNF-antagonists, including Cimzia. Many of these patients were taking concomitant immunosuppressants (e.g. MTX, corticosteroids). Some of these patients required hospitalization. Most patients had improvement of their psoriasis following discontinuation of their TNF-antagonist. Some patients have had recurrences of the psoriasis when they were rechallenged with a different TNF-antagonist. Discontinuation of Cimzia should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Use in the elderly
Specific clinical studies have not been performed in elderly subjects. However, no effect of age was observed in a population pharmacokinetic analysis in patients with rheumatoid arthritis in which 78 subjects (13.2% of the population) were aged 65 or greater and the oldest subject was aged 83 years. There was an apparently higher incidence of infections among subjects ≥ 65 years of age.

Paediatric use
The safety and efficacy of Cimzia in paediatric patients have not been established.

Effects on laboratory tests

Activated partial thromboplastin time (aPTT) assay
Interference with certain coagulation assays has been detected in patients treated with Cimzia. Cimzia may cause erroneously elevated 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 HemosIL lyophilised silica tests from Instrumentation Laboratories. Other aPTT assays may be affected as well. There is no evidence that Cimzia therapy has an effect on coagulation *in vivo.* After patients receive Cimzia, careful attention should be given to interpretation of abnormal coagulation results. Interference with thrombin time (TT) and prothrombin time (PT) assays have not been observed.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Concomitant drug treatment with methotrexate, corticosteroids, nonsteroidal anti-inflammatory drugs, analgesics, 5-amino salicylic acid analogs or anti-infectives had no effect on the pharmacokinetics of Cimzia.

The pharmacokinetics of Cimzia were evaluated in a pharmacokinetic interaction study in 16 patients with rheumatoid arthritis receiving stable doses of methotrexate (ranging from 5 to 17.5 mg per week). Coadministration of Cimzia with methotrexate had no significant effect on the pharmacokinetics of methotrexate while the pharmacokinetics of Cimzia were similar to those observed previously in healthy subjects.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Since Cimzia does not cross react with mouse or rat TNFα, reproductive studies have been performed in rats using a rodent antimurine TNFα PEGylated Fab' fragment (cTN3 PF), similar to Cimzia. cTN3 PF had no effects on the fertility and general reproductive performance of male and female rats at IV doses up to 100 mg/kg, administered twice weekly.

Effects on sperm motility measures and a trend of reduced sperm count in male rodents have been observed with no apparent effect on fertility.

In a clinical trial to assess the effect of certolizumab pegol on semen quality parameters (primary variables: % total motility and % normal ovoid form morphology; secondary variables; semen volume, sperm count and concentration, % progressive motility, and % vitality), 20 healthy male subjects were randomized to receive a single subcutaneous dose of 400 mg of certolizumab pegol (n = 15) or placebo (n = 5). A linear repeated measures model with the interaction between treatment group (placebo or certolizumab pegol) and visit as fixed effect and subject as random effect was fitted to each variable. The 90% confidence intervals on the treatment effect were derived. During the 14 weeks follow-up certolizumab pegol 400 mg treatment had no effect over that of placebo on semen quality variables (total motility point estimate -1.3, 90% CI -8.5 to 5.9; morphology point estimate -2.1, 90% CI -4.7 to 0.4).

Use in pregnancy
(Category C)

Data from the Cimzia pharmacovigilance database on reported pregnancies were analysed. Among those, 1392 were reported from prospective pregnancies with known outcomes of which 1021 were exposed to Cimzia at least during the first trimester. Although these data should be interpreted with caution due to its methodological limitations (such as incomplete information, lack of control group and underreporting) and are not sufficient to conclude with reasonable certainty that there is no increased risk of malformation, no increased risk of major birth defects or other adverse pregnancy outcomes were observed.

Clinical pharmacokinetic studies in women exposed during the third trimester have shown no to minimal placental transfer of certolizumab pegol from mother to infant.

If Cimzia is used during pregnancy, a benefit risk assessment, including the potential effect on the normal immune response in the newborn (see below) should be performed.

All women of childbearing age with rheumatic diseases should have a discussion around contraception and adequate contraception should be advised. The elimination of certolizumab pegol may take up to 5 months and should be considered in pre-pregnancy counselling.

<u>Clinical data</u>
In a multicentre clinical study 16 women were prescribed Cimzia at a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks during pregnancy. The last dose of Cimzia was given on average 11 days prior to delivery (range 1-27 days). Certolizumab pegol plasma concentrations were measured in samples from the mothers and infants using a validated assay with a Lower Limit of Quantification (LLOQ) of 0.032µg/ml. Certolizumab pegol plasma concentrations measured in the mothers at delivery (range: 4.96 – 49.4 µg/ml) were consistent with the observed plasma concentrations in non-pregnant women in study RA-I. Certolizumab pegol plasma concentrations measured in 14 infants at birth were Below the Limit of Quantification (BLQ) in 13 samples; one was 0.042 µg/ml with an infant/mother plasma ratio at birth of 0.09%. At Week 4 and Week 8, all infant

concentrations were BLQ. The plasma concentration of total PEG in the umbilical cords at birth was BLQ for 14 of the 15 samples.

In an independent clinical study in 10 patients with Crohn's disease treated with Cimzia, using a less specific and sensitive assay, certolizumab pegol concentrations were measured in maternal blood as well as in cord and infant blood (n=12) at the day of birth. Certolizumab pegol concentrations were very low in cord blood (<0.41 [Lower Level of Quantification] – 1.66 µg/mL) and infant blood (<0.41 – 1.58 µg/mL) compared to maternal blood levels (1.87 – 59.57 µg/mL). PEG concentrations were below Lower Level of Quantification, which ranged from 9 µg/mL (when sufficient sample was collected) up to 36 µg/mL (when sample needed to be diluted), in all cord and infant blood samples.

Non-clinical data

Animal studies using a rodent anti-rat TNFα reagent did not reveal evidence of harm to the foetus. However, these are insufficient with respect to human reproductive toxicity.

Active placental transfer of IgGs is mediated by the Fc part of an antibody binding to the neonatal Fc receptor (FcRn). Certolizumab pegol consists of just the Fab part of an antibody and does not contain an Fc part. In reproduction studies in rats cTN3 γ1 (a surrogate full antibody to certolizumab including an Fc part) was transferred to the foetus during gestation. However, there was little or no measurable transfer of cTN3 PF (surrogate Fab' fragment to certolizumab without an Fc) to the foetus when compared to maternal plasma concentrations, demonstrating the importance of the Fc for placental transfer.

Information from case reports of certolizumab pegol exposure during pregnancy

As of November 1, 2020, 1392 prospective pregnancies with known outcomes have been reported in women exposed to Cimzia from clinical studies and post-marketing surveillance of which 1021 were exposed to Cimzia during the first trimester. These 1392 prospective pregnancies resulted in 1259 live births (88.4% of all 1425 outcomes), 150 spontaneous or induced abortions (10.5%), 5 ectopic pregnancies (0.35%) and 11 stillbirths (0.8%). 26 major birth defects (2.1%) were reported among the 1259 live births with no discernible pattern in the reported malformations. Two foetal major congenital abnormalities led to medically induced abortion.

Published data from the US population suggested that major birth defects occur in 2-4% of the general population and that miscarriage occurs in 15-20% of clinically recognized pregnancies. In the EU general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-3% and 10-25% respectively.

Clinical considerations

Disease-Associated Maternal and /or Embryo/Foetal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with chronic inflammatory diseases (including rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, or Crohn's disease) is correlated with maternal disease activity and that active disease increases the risk of adverse pregnancy outcomes, including foetal loss, preterm delivery (before 37 weeks of gestation), low birth weight (<2500 g), pre-eclampsia and small for gestational age at birth.

Foetal / Neonatal Adverse Reactions

TNF-antagonists administered during pregnancy could affect normal immune responses in the newborn. The clinical significance of BLQ or low levels is unknown for in utero exposed infants. The theoretical risk of administration of live or live-attenuated vaccines to the infants exposed in utero to Cimzia should be weighed against the benefits of vaccinations.

Use in lactation
In a multicentre clinical study in 17 lactating women treated with Cimzia, no to minimal transfer of certolizumab pegol from the plasma to breast milk was observed. The highest concentration measured in milk at any time point was < 1% of the mean expected plasma concentration of a maintenance therapeutic dose in adults.

Samples were obtained from breast milk in women who were at least 6 weeks post-partum and had received at least 3 consecutive doses of Cimzia 200 mg every 2 weeks or 400 mg every 4 weeks, pre-injection (Day 0 of the sampling period, Cimzia dosing day) then on Days 2, 4, 6, 8, 10, 12 and 14 (for Cimzia 200 mg every 2 weeks dosing; pre-injection) and on or about Day 28 (for Cimzia 400 mg every 4 weeks dosing; pre-injection). The concentration of certolizumab pegol was BLQ (<0.032µg/ml) in 77 (56%) of the 137 breast milk samples. The concentration of certolizumab pegol ranged from BLQ to a maximum of 0.0758 µg/ml.

The median estimated average daily infant dose (ADID) which represents an average amount of certolizumab pegol that the infant may potentially consume daily over the dosing interval was 0.0035 mg/kg/day (range: 0 - 0.0104 mg/kg/day). Using the ADID, the percentage of the maternal Cimzia dose that reaches an infant in a typical 24-hour period, known as the relative infant dose (RID) was calculated; the RID ranged from 0.04% to 0.30%.

Published data suggest that the systemic exposure to a breastfed infant is expected to be low because certolizumab pegol is a protein that is degraded in the gastrointestinal tract after oral administration, leading to an expected very low absolute bioavailability.

From a safety perspective, the 17 infants in the study experienced clinical events similar to those occurring in a general population of similar age.

In a separate study, plasma certolizumab pegol levels were collected 4 weeks after birth in 9 infants who were exclusively or non-exclusively breastfed by mothers taking Cimzia. The amount of certolizumab pegol measured was BLQ in all infant plasma samples.

Cimzia can be used during breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive use machines have been performed. Cimzia may have a minor influence on the ability to drive and use machines. Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of Cimzia.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Rheumatoid arthritis
Cimzia was studied in 4049 patients with rheumatoid arthritis in controlled and open label trials for up to 92 months. The data in Table 3 are based primarily on adverse reactions reported in placebo controlled rheumatoid arthritis studies involving the 2965 patients receiving Cimzia and 1137 patients receiving placebo during the controlled period. For placebo controlled and open label adverse drug reactions, all events recorded with causality at least possibly related to study medication were considered.

In the placebo controlled studies, patients receiving Cimzia had an approximately 4 times greater duration of exposure compared with the placebo group. This difference in exposure is primarily due to patients on placebo being more likely to withdraw early. In addition, studies RA-I and RA-II had a mandatory withdrawal for nonresponders at Week 16, the majority of who were on placebo. Adverse reactions were reported in 34.0% of patients treated with Cimzia and 24.9% of patients treated with

placebo in rheumatoid arthritis controlled clinical trials. The proportion of patients who discontinued treatment due to adverse events during the controlled trials was 4.4% for patients treated with Cimzia and 2.7% for patients treated with placebo.

In the placebo controlled rheumatoid arthritis studies, the most common types of adverse reactions were infections reported in 14.4% of patients on Cimzia and 8.0% of patients on placebo, general disorders and administration site conditions, reported in 8.8% of patients on Cimzia and 7.4% of patients on placebo and skin and subcutaneous tissue disorders, reported in 7.0% of patients with Cimzia and 2.4% of patients on placebo.

Cimzia in combination with MTX was studied in 879 (3 subjects were randomised but did not receive the study medication) DMARD naïve patients with rheumatoid arthritis in a placebo + MTX controlled clinical trial (C-EARLY) for up to 52 weeks. The safety profile for the DMARD naïve patients with rheumatoid arthritis treated with Cimzia is summarised in Table 4 and Hepatic section.

Psoriatic arthritis
Cimzia was studied in 409 patients with psoriatic arthritis in a placebo controlled clinical trial (PsA001). The safety profile for psoriatic arthritis patients treated with Cimzia was consistent with the safety profile in rheumatoid arthritis and previous experience with Cimzia.

Non-radiographic axial spondyloarthritis and Ankylosing spondylitis
Cimzia was initially studied in 325 patients with axial spondyloarthritis (including ankylosing spondylitis and non-radiographic axial spondyloarthritis) in a placebo controlled clinical trial (AS001). Cimzia was subsequently studied in 317 patients with non-radiographic axial spondyloarthritis (AS0006). Cimzia was also studied in patients with axial spondyloarthritis (including ankylosing spondylitis and non-radiographic axial spondyloarthritis) in a clinical study for up to 96 weeks, which included a 48-week open-label run-in phase (N=736) followed by a 48-week placebo-controlled phase (N = 313) for patients in sustained remission (AS0005). In all 3 studies, the safety profile for these patients treated with Cimzia was similar to the safety profile seen in patients with rheumatoid arthritis and previous experience with Cimzia.

Plaque psoriasis
Cimzia was studied in 1112 patients with psoriasis in controlled and open label studies (Phase 2 and Phase 3) for up to 3 years. The Phase 3 program included a 16-week placebo controlled phase, including a 12-week active comparator-controlled phase in one of the 3-year studies, followed by a 32-week dose-blind period and a 96-week open-label treatment period. The data in Table 5 are based on adverse events in the psoriasis phase 3 studies through Week 16 (157 on placebo and 692 on Cimzia). Adverse events reported in these studies from Week 16 to Week 48 (82 placebo and 888 on Cimzia) are summarised in Table 6. The long-term safety profile of Cimzia 400 mg every 2 weeks and Cimzia 200 mg every 2 weeks was generally similar and was consistent with previous experience with Cimzia.

During controlled Phase 2 and Phase 3 clinical trials through Week 16, the proportion of patients with serious adverse events was 3.5 % for Cimzia and 3.7 % for placebo.

The most common adverse reactions reported in controlled clinical studies through Week 16 belonged to the system organ classes Infections and infestations, reported in 6.1 % of patients on Cimzia and 7 % of patients on placebo, General disorders and administration site conditions, reported in 4.1 % of patients on Cimzia and 2.3 % of patients on placebo, and Skin and subcutaneous tissue disorders, reported in 3.5% of patients on Cimzia and 2.8 % of patients on placebo. The proportion of patients

who discontinued treatment due to adverse events in the controlled clinical studies was 1.5% for patients treated with Cimzia and 1.4% for patients treated with placebo.

Table 3: Summary of Adverse Events Regardless of Causality for event incidence ≥ 1% in the all CZP doses group and exceeding that of the placebo group reported during placebo-controlled RA clinical trials in patients with inadequate response to DMARDs.

System Organ Class	Adverse Event	PBO +/- MTX (n=1137) (%)	CZP +/- MTX (n=2965) (%)
Infections and infestations	Upper respiratory tract infection	4.3%	5.9%
	Nasopharyngitis	4.1%	5.3%
	Urinary tract infection	4.1%	4.5%
	Herpes simplex	0.7%	2.3%
	Sinusitis	1.6%	2.2%
	Pharyngitis	0.6%	1.7%
	Bronchitis acute	0.5%	1.6%
	Rhinitis	0.6%	1.6%
	Bacteriuria	0.6%	1.0%
Musculoskeletal and connective tissue disorders	Back pain	1.3%	3.3%
	Muscle spasms	0.9%	1.4%
Gastrointestinal disorders	Abdominal pain upper	0.9%	1.3%
	Abdominal pain	0.6%	1.3%
General disorders and administration site conditions	Injection site reactions	0.8%	1.4%
	Pyrexia	1.1%	2.2%
	Injection site erythema	0.7%	1.2%
Skin and subcutaneous tissue disorders	Pruritus	0.6%	1.6%
	Rash	1.1%	3.5%
Investigations	Aspartate aminotransferase increased	1.1%	1.2%
	Alanine aminotransferase increased	1.4%	1.8%
	Hepatic enzyme increased	0.8%	1.1%
Respiratory, thoracic and mediastinal disorders	Cough	2.6%	2.7%
Injury, poisoning and procedural complications	Contusion	0.5%	1.1%
Vascular disorders	Hypertension	1.4%	3.9%
Blood and Lymphatic system disorders	Eosinophilia	0.4%	1.0%
Renal and urinary disorders	Haematuria	0.6%	1.0%

Table 4: Summary of Adverse Events Regardless of Causality for event incidence ≥ 1% in the CZP group and exceeding that of the placebo group reported during C-EARLY clinical trial (DMARD naïve patients with rheumatoid arthritis in a placebo-controlled clinical trial).

System Organ Class	Adverse Event	PBO + MTX (n=217) (%)	CZP + MTX (n=659) (%)
Infections and infestations	Upper respiratory tract infection	5.1%	10.9%
	Nasopharyngitis	6.0%	7.0%
	Tooth abscess	0.5%	1.1%
	Conjunctivitis	0.0%	1.2%
	Oral herpes	0.9%	1.5%
	Herpes zoster	0.9%	1.1%
	Influenza	1.4%	2.1%
	Bronchitis	3.2%	4.4%
	Sinusitis	2.3%	3.6%
Ear and labyrinth disorders	Vertigo	0.5%	1.1%
Musculoskeletal and connective tissue disorders	Back pain	2.8%	2.9%
	Myalgia	0.9%	1.1%
	Muscle spasms	0.9%	1.1%
	Arthralgia	1.8%	2.1%
	Pain in extremity	0.5%	1.7%
	Osteoarthritis	0.9%	1.5%
Gastrointestinal disorders	Abdominal pain upper	1.8%	2.1%
	Diarrhoea	1.8%	4.7%
	Gastritis	0.9%	2.1%
	Nausea	10.1%	12.6%
	Vomiting	1.4%	2.0%
	Mouth ulceration	1.4%	1.5%
	Stomatitis	0.0%	1.1%
	Abdominal pain	0.9%	2.3%
General disorders and administration site conditions	Injection site reaction	0.0%	1.1%
	Pyrexia	0.9%	1.5%
	Fatigue	0.0%	2.1%
	Malaise	0.5%	1.5%
	Injection site bruising	0.9%	1.2%
	Alopecia	3.2%	3.9%
	Dermatitis	0.9%	1.1%
Investigations	Aspartate aminotransferase increased	2.3%	3.0%
	Alanine aminotransferase increased	4.1%	6.4%
Investigations	Blood creatine phosphokinase increased	0.5%	2.0%
	Hypercholesterolaemia	2.3%	3.0%
	Hyperlipidaemia	0.9%	1.4%
Respiratory, thoracic and mediastinal disorders	Cough	3.2%	3.9%
	Epistaxis	0.0%	1.4%
Injury, poisoning and procedural complications	Contusion	0.5%	1.4%
	Fall	0.9%	1.1%
	Laceration	0.5%	1.5%

System Organ Class	Adverse Event	PBO + MTX (n=217) (%)	CZP + MTX (n=659) (%)
Nervous system disorders	Headache	3.7%	6.8%
	Paraesthesia	0.0%	1.1%
Vascular disorders	Hypertension	2.3%	2.4%
	Anaemia	1.4%	2.6%
Immune system disorders	Seasonal allergy	0.0%	1.7%
Renal and urinary disorders	Haematuria	0.0%	1.0%
Reproductive system and breast disorders	Menorrhagia	0.0%	1.1%
Psychiatric disorders	Anxiety	0.5%	1.2%

Table 5: Summary of Adverse Events Regardless of Causality reported for event incidence ≥1 % in the CZP dose groups and exceeding that of placebo group reported during psoriasis phase 3 studies (CIMPASI-1, CIMPASI-2, CIMPACT) through Week 16

Primary System Organ Class Adverse Event (Preferred Term)	Placebo (N=157) n (%)	CIMZIA 200 mg Q2W (N=350) n (%)	CIMZIA 400 mg Q2W (N=342) n (%)
Gastrointestinal disorders			
Abdominal pain	0	2 (0.6)	5 (1.5)
Abdominal pain upper	1 (0.6)	4 (1.1)	2 (0.6)
Dyspepsia	1 (0.6)	1 (0.3)	4 (1.2)
General disorders and administration site conditions			
Fatigue	3 (1.9)	4 (1.1)	8 (2.3)
Injection site reaction	0	4 (1.1)	6 (1.8)
Oedema peripheral	0	5 (1.4)	2 (0.6)
Immune system disorders			
Seasonal allergy	0	4 (1.1)	0
Infections and infestations			
Bronchitis	1 (0.6)	3 (0.9)	7 (2.0)
Influenza	1 (0.6)	1 (0.3)	4 (1.2)
Nasopharyngitis	19 (12.1)	42 (12.0)	43 (12.6)
Oral herpes	0	3 (0.9)	4 (1.2)
Pharyngitis	0	6 (1.7)	4 (1.2)
Rhinitis	0	2 (0.6)	8 (2.3)
Sinusitis	2 (1.3)	8 (2.3)	3 (0.9)
Urinary tract infection	2 (1.3)	4 (1.1)	5 (1.5)
Viral upper respiratory tract infection	1 (0.6)	8 (2.3)	8 (2.3)
Injury, poisoning and procedural complications			
Contusion	1 (0.6)	0	4 (1.2)
Investigations			
Alanine aminotransferase increased	0	10 (2.9)	3 (0.9)
Aspartate aminotransferase increased	0	8 (2.3)	2 (0.6)
Blood creatine phosphokinase increased	2 (1.3)	2 (0.6)	8 (2.3)
Transaminases increased	0	2 (0.6)	4 (1.2)
Nervous system disorders			
Headache	3 (1.9)	10 (2.9)	13 (3.8)
Respiratory, thoracic and mediastinal disorders			
Cough	3 (1.9)	4 (1.1)	11 (3.2)
Oropharyngeal pain	0	4 (1.1)	4 (1.2)

Primary System Organ Class Adverse Event (Preferred Term)	Placebo (N=157) n (%)	CIMZIA 200 mg Q2W (N=350) n (%)	CIMZIA 400 mg Q2W (N=342) n (%)
Skin and subcutaneous tissue disorders			
Alopecia	0	1 (0.3)	5 (1.5)

Q2W= Every two weeks

Table 6: Summary of Adverse Events Regardless of Causality reported for event incidence ≥1 % in the CZP dose groups and exceeding that of placebo group reported during psoriasis phase 3 studies (CIMPASI-1, CIMPASI-2, CIMPACT) Week 16 to Week 48

Primary System Organ Class Adverse Event (Preferred Term)	Placebo (N=82) n (%)	CIMZIA 200 mg Q2W (N=348) n (%)	CIMZIA 400 mg Q2W (N=540) n (%)
Gastrointestinal Disorders			
Diarrhoea	1 (1.2)	6 (1.7)	9 (1.7)
Nausea	0	3 (0.9)	6 (1.1)
General disorders and administration site conditions			
Fatigue	0	2 (0.6)	6 (1.1)
Pyrexia	0	2 (0.6)	8 (1.5)
Infections and infestations			
Bronchitis	1 (1.2)	4 (1.1)	9 (1.7)
Conjunctivitis	0	2 (0.6)	9 (1.7)
Nasopharyngitis	10 (2.2)	49 (14.1)	82 (15.2)
Oral herpes	1 (1.2)	6 (1.7)	3 (0.6)
Pharyngitis	0	8 (2.3)	3 (0.6)
Sinusitis	1 (1.2)	6 (1.7)	9 (1.7)
Urinary tract infection	0	9 (2.6)	6 (1.1)
Viral upper respiratory tract infection	1 (1.2)	8 (2.3)	2 (0.4)
Injury, poisoning and procedural complications			
Contusion	1 (1.2)	3 (0.9)	7 (1.3)
Muscle strain	0	6 (1.7)	1 (0.2)
Investigations			
Alanine aminotransferase increased	1 (1.2)	7 (2.0)	8 (1.5)
Aspartate aminotransferase increased	1 (1.2)	6 (1.7)	9 (1.7)
Blood creatine phosphokinase increased	1 (1.2)	8 (2.3)	6 (1.1)
Gamma-glutamyltransferase increased	1 (1.2)	2 (0.6)	10 (1.9)
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (1.2)	13 (3.7)	9 (1.7)
Back pain	0	11 (3.2)	14 (2.6)
Spinal pain	0	0	8 (1.5)
Nervous system disorders			
Headache	2 (2.4)	10 (2.9)	16 (3.0)
Respiratory, thoracic and mediastinal disorders			
Cough	1 (1.2)	8 (2.3)	4 (0.7)
Oropharyngeal pain	0	3 (0.9)	9 (1.7)
Skin and subcutaneous tissue disorders			
Dermatitis	0	4 (1.1)	4 (0.7)

Q2W= Every two weeks

Note: Subjects were included in the treatment group based on the dose they were assigned to receive at Week 16, including subjects who entered the escape arm at Week 16 and received CZP 400mg Q2W.

Note: Data collected during treatment with the CZP 400mg Q4W dose in CIMPACT were summarized under the CZP 200mg Q2W treatment group as they are the same cumulative monthly dose.

Note: Of the 82 subjects who received placebo treatment during week 16 to week 48, 71 subjects received either CZP 200mg Q2W, CZP 400mg Q2W or Enbrel through Week 16 in the CIMPACT study.

Within the organ system classes, adverse reactions by frequency are listed using the following categories: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), not known (cannot be estimated from the available data) in Table 7.

Table 7: Adverse drug reactions in clinical trials and postmarketing

System Organ Class	Frequency	Adverse Drug Reactions
Infections and infestations	Common	bacterial infections (including abscess), viral infections (including herpes zoster and herpes simplex, papillomavirus, influenza)
	Uncommon	sepsis (including multi-organ failure, septic shock), tuberculosis (including miliary, disseminated and extrapulmonary disease), fungal infections (includes opportunistic)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon	blood and lymphatic system malignancies (including lymphoma and leukaemia), solid organ tumours, non-melanoma skin cancers, pre-cancerous lesions (including oral leukoplakia, melanocytic nevus), benign tumours and cysts (including skin papilloma)
	Rare	gastrointestinal tumours, melanoma
	Not Known	Merkel cell carcinoma*, Kaposi's sarcoma
Blood and the lymphatic system disorders	Common	eosinophilic disorders, leukopaenia (including neutropaenia, lymphopaenia)
	Uncommon	anaemia, lymphadenopathy, thrombocytopaenia, thrombocytosis
	Rare	pancytopaenia, splenomegaly, erythrocytosis, white blood cell morphology abnormal
Immune system disorders	Uncommon	vasculitides, lupus erythematosus, drug hypersensitivity (including anaphylactic shock), allergic disorders, autoantibody positive
	Rare	angioneurotic oedema, sarcoidosis, serum sickness, panniculitis (including erythema nodosum)
Endocrine disorders	Rare	thyroid disorders
Metabolism and nutrition disorders	Uncommon	electrolyte imbalance, dyslipidaemia, appetite disorders, weight change
	Rare	haemosiderosis
Psychiatric disorders	Uncommon	anxiety and mood disorders (including associated symptoms)
	Rare	suicide attempt, delirium, mental impairment
Nervous system disorders	Common	headaches (including migraine), sensory abnormalities
	Uncommon	peripheral neuropathies, dizziness, tremor
	Rare	seizure, cranial nerve inflammation, impaired coordination or balance, sleep disorder, multiple sclerosis
	Not Known	Guillain-Barré syndrome*
Eye disorders	Uncommon	visual disorder (including decreased vision), eye and eyelid inflammation, lacrimation disorder
Ear and labyrinth disorders	Uncommon	tinnitus, vertigo
Cardiac disorders	Uncommon	cardiomyopathies (including heart failure), ischaemic coronary artery disorders, arrhythmias (including atrial fibrillation), palpitations
	Rare	pericarditis, atrioventricular block
Vascular disorders	Common	hypertension
	Uncommon	haemorrhage or bleeding (any site), hypercoagulation (including thrombophlebitis, pulmonary embolism), syncope, oedema (including peripheral, facial), ecchymoses (including haematoma, petechiae)
	Rare	cerebrovascular accident, arteriosclerosis, Raynaud's phenomenon, livedo reticularis, telangiectasia
Respiratory, thoracic and mediastinal disorders	Uncommon	asthma and related symptoms, pleural effusion and symptoms, respiratory tract congestion and inflammation, cough
	Rare	interstitial lung disease, pneumonitis

Gastrointestinal disorders	Common	nausea
	Uncommon	ascites, gastrointestinal ulceration and perforation, gastrointestinal tract inflammation (any site), stomatitis, dyspepsia, abdominal distension, oropharyngeal dryness
	Rare	odynophagia, hypermotility
Hepatobiliary disorders	Common	hepatitis (including hepatic enzyme increased)
	Uncommon	hepatopathy (including cirrhosis), cholestasis, blood bilirubin increased
	Rare	cholelithiasis
Skin and subcutaneous tissue disorders	Common	rash
	Uncommon	alopecia, new onset or worsening of psoriasis (including palmoplantar pustular psoriasis) and related conditions, dermatitis and eczema, sweat gland disorder, skin ulcer, photosensitivity, acne, skin discolouration, dry skin, nail and nail bed disorders
	Rare	skin exfoliation and desquamation, bullous conditions, hair texture disorder, Stevens-Johnson syndrome^, erythema multiforme^, lichenoid reactions
Musculoskeletal, connective tissue and bone disorders	Uncommon	muscle disorders, blood creatine phosphokinase increased
Renal and urinary disorders	Uncommon	renal impairment, blood in urine, bladder and urethral symptoms
	Rare	nephropathy (including nephritis)
Reproductive system and breast disorders	Uncommon	menstrual cycle and uterine bleeding disorders (including amenorrhea), breast disorders
	Rare	sexual dysfunction
General disorders and administration site conditions	Common	pyrexia, pain (any site), asthaenia, pruritus (any site), injection site reactions
	Uncommon	chills, influenza-like illness, altered temperature perception, night sweats, flushing
	Rare	fistula (any site)
Investigations	Uncommon	blood alkaline phosphatase increased, coagulation time prolonged
	Rare	blood uric acid increased
Injury, poisoning and Procedural complications	Uncommon	skin injuries, impaired healing

*These events have been related to the class of TNF-antagonists, but incidence with Cimzia is not known.
^ The causal relationship with CIMZIA is not established but these events are known as class effect of TNF-antagonists.

The additional following Adverse Drug Reactions (ADRs) have been observed uncommonly with Cimzia in other indications: gastrointestinal stenosis and obstructions, general physical health deterioration, grand mal convulsion, optic neuritis, abortion spontaneous and azoospermia, vaginal discharge and fistula (any site).

Infections
The incidence of new cases of infections in placebo controlled clinical studies in rheumatoid arthritis was 1.03 per patient year for all Cimzia treated patients and 0.92 per patient year for placebo treated patients. The infections consisted primarily of upper respiratory tract infections, urinary tract infections, lower respiratory tract infections and herpes viral infections.

In the placebo controlled studies, there were more new cases of serious infection adverse reactions in the Cimzia treatment groups, compared with the placebo groups (0.07 per patient year for all Cimzia doses vs. 0.02 per patient year for placebo). Rates of serious infections were 0.08 per patient year in the 200 mg every 2 week dose group and 0.05 in the 400 mg every 4 weeks dose group. Serious infections included tuberculosis and invasive opportunistic infections (e.g. Pneumocystis, fungal oesophagitis, Nocardia and herpes zoster disseminated). There is no evidence of increased risk of

infections with continued exposure over time (see Section 4.4 Special Warnings and Precautions for Use).

The incidence rate of new cases of infections in controlled clinical trials in psoriasis was 1.37 per patient-year for all Cimzia treated patients and 1.59 per patient-year for placebo-treated patients. The infections consisted primarily of upper respiratory tract infections and viral infections (including herpes infections). The incidence of serious infections was 0.02 per patient-year in Cimzia treated patients. No serious infections were reported in the placebo-treated patients. There is no evidence of an increased risk of infections with continued exposure over time.

Tuberculosis and opportunistic infections
In completed and ongoing global clinical studies in all indications 5118 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. Across all indications, no cases of TB have been reported in Australia (0/140) and 1 case (1/53) in New Zealand. In total across the region and all indications, this represents 1 case among 193 patients. 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 50 cases of TB among 4049 exposed patients; including some fatal cases. In Phase 2 and Phase 3 studies with Cimzia in plaque psoriasis, there were 2 cases of TB among 1112 exposed patients (see Section 4.4 Special Warnings and Precautions for Use).

Heart failure
In placebo controlled and open label clinical trials, 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 Section 4.4 Special Warnings and Precautions for Use).

Hepatic
In placebo controlled rheumatoid arthritis studies, the adverse events of ALT increased occurred in 1.8% of Cimzia treated and 1.4% of placebo treated patients, and AST increased occurred in 1.2% of Cimzia treated and 1.1% of placebo treated patients. Hepatic adverse events occurred in 1.2% of Cimzia treated patients and 0.7% of placebo treated patients. In placebo controlled and open label rheumatoid arthritis studies combined, the incidence of hepatic adverse events in Cimzia treated patients was 1.88 per 100 patient years, as compared to 2.88 per 100 patient years during the placebo controlled rheumatoid arthritis studies. In the C-EARLY study, the incidence of adverse events of ALT increased occurred in 6.4% and 4.1%, of AST increased in 3.0% and 2.3% and of hepatic enzyme increased in 2.4% and 2.8% in Cimzia treated and placebo treated patients respectively, in DMARDs naïve subjects. Of note is that the MTX dose was higher in C-EARLY study compared to RA-I, RA-II and RA-IV.

Immunogenicity

The data below reflect the percentage of patients whose test results were considered positive for antibodies to certolizumab pegol in an ELISA and later in a more sensitive method 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 in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Rheumatoid arthritis
The overall percentage of patients with antibodies to Cimzia detectable on at least one occasion was 8% (105 of 1509) in the phase III RA placebo controlled trials. The percentage of patients with antibodies to Cimzia at 6 months, for each of the approved dosing regimens, was 5.1% and 8.5% for the 200 mg every 2 weeks + MTX regimen (studies RA-I and RA-II respectively), 4% for the 400 mg every 4 weeks + MTX regimen (Study RA-IV), and 22.5% for the 400 mg every 4 weeks monotherapy regimen (Study RA-III).

Approximately one-third of antibody positive patients (3%, 39 of 1509) had antibodies with neutralising activity *in vitro.* Patients treated with concomitant immunosuppressants (MTX) had a lower rate of antibody development than patients not taking immunosuppressants at baseline (2% vs 8%).

Antibody formation was associated with lowered drug plasma concentration and in some patients, reduced efficacy. No association was seen between antibody development and the development of adverse events.

Psoriatic arthritis
The overall percentage of patients with antibodies to Cimzia detectable on at least one occasion up to Week 24 was 11.7% in the phase III placebo controlled trial in patients with psoriatic arthritis. Antibody formation was associated with lowered drug plasma concentration. The number of patients with antibodies to Cimzia in this trial was too small to make valid assessment of the impact of the antibody formation on efficacy.

Plaque psoriasis
In the Phase 3 placebo and active controlled studies, the percentages of patients who were positive for anti-certolizumab pegol antibodies on at least one occasion during treatment up to Week 48 were 8.3 % (22/265) and 19.2% (54/281) for the Cimzia 400 mg every 2 weeks and Cimzia 200 mg every 2 weeks respectively. In CIMPASI-1 and CIMPASI-2, sixty patients were antibody positive, 27 of these patients were evaluable for neutralizing antibodies and tested positive. Anti-certolizumab antibody positivity was associated with lowered drug plasma concentration and in some patients with reduced efficacy.

Non-radiographic axial spondyloarthritis and axial spondyloarthritis
The overall percentage of patients with antibodies to Cimzia detectable on at least one occasion up to Week 24 was 4.4% in the phase III placebo controlled trial (AS001) in patients with axial spondyloarthritis. Antibody formation was associated with lowered drug plasma concentration. The number of patients with antibodies to Cimzia in these trials was too small to make valid assessment of the impact of the antibody formation on efficacy.

A more sensitive and drug tolerant assay was used for the first time in the AS0006 study (and later also in the AS0005 study), resulting in a greater proportion of samples having measurable antibodies to certolizumab pegol and thus a greater incidence of patients being classed as antibody positive. In AS0006, after up to 52 weeks of treatment, the overall incidence of patients who were antibody positive to certolizumab pegol was 97% (248/255 patients). Of these antibody positive patients, only

the highest titers were associated with reduced certolizumab pegol plasma levels. However, no impact on efficacy was observed in patients with high titers. Of the patients who were anti-certolizumab pegol antibody positive at any time, about 22% (54/248), had antibodies that were classified as neutralizing.

Similar results were seen in AS0005. Results from AS0005 also indicated that a reduction of the dose to Cimzia 200 mg every 4 weeks did not change immunogenicity outcomes.

Hypersensitivity reactions
The following symptoms that could be compatible with hypersensitivity reactions have been reported following Cimzia administration to patients: angioedema, dermatitis allergic, urticaria, dyspnea, hot flush, hypotension, injection site reactions, malaise, pyrexia, rash, serum sickness, and (vasovagal) syncope (see Section 4.4 Special Warnings and Precautions for Use).

Malignancies and lymphoproliferative disorders
In placebo controlled and open label rheumatoid arthritis studies combined, observed malignancies included breast and ovarian cancers, basal cell carcinoma, and lymphoma. Cases of lymphoma occurred at an incidence rate of 0.05 per 100 patient years and melanoma at an incidence rate of 0.08 per 100 patient years with Cimzia in rheumatoid arthritis clinical trials. The number of cases reported is insufficient to identify a treatment effect (see Section 4.4 Special Warnings and Precautions for Use).

In controlled and open-label psoriasis phase II and III clinical studies, malignancies (excluding non-melanoma skin cancer) were observed at an incidence rate of 0.44 per 100 patient-years among 1112 Cimzia treated-patients.

Excluding non-melanoma skin cancer, 11 malignancies including 1 case of lymphoma were observed in the Cimzia psoriasis clinical trials in which a total of 1112 patients were treated, representing 2300 patient-years.

Lymphoma
In rheumatoid arthritis placebo controlled and open label studies combined, 5 cases of lymphoma were reported in patients treated with Cimzia (1 case in the placebo controlled studies and 4 in the open label studies), corresponding to a rate of 0.05/100 patient years among 4049 patients. No lymphoma was reported among 1137 placebo treated patients. One case of lymphoma was also observed in the phase III psoriatic arthritis clinical trial.

Non-lymphoma malignancies
In the rheumatoid arthritis placebo controlled studies, 9 patients (0.3%) treated with Cimzia and 4 patients (0.35%) in the placebo group experienced malignancies other than lymphomas and non-melanoma skin cancers.

In rheumatoid arthritis placebo controlled and open label studies combined, 68 malignancies other than lymphomas and non-melanoma skin cancers were observed at a rate of 0.7/100 patient years among 4049 Cimzia treated patients and 4 malignancies at a rate of 1.08/100 patient years among 1137 placebo treated patients.

Non-melanoma skin cancers
In the rheumatoid arthritis placebo controlled studies, non-melanoma skin cancers occurred in 4

patients (0.1%) receiving Cimzia and 1 patient in the placebo group. In the controlled and uncontrolled studies, there were a total of 28 (0.7%) subjects who experienced nonmelanoma skin cancers.

Autoimmune disease
In the pivotal placebo controlled rheumatoid arthritis studies, there was no clinically meaningful increase in ANA or anti-double stranded DNA antibody conversion noted for Cimzia treated patients at any dose. For subjects who were ANA negative at baseline, 16.7% of those treated with Cimzia developed positive ANA titers, compared with 12.0% of subjects in the placebo group. Taking into account the difference in exposure between the 2 groups, there is no increased risk of developing a positive ANA with Cimzia treatment. In both placebo controlled and open label follow-up studies for rheumatoid arthritis, cases of lupus-like syndrome were reported uncommonly. There have been rare reports of other immune mediated conditions; the causal relationship to Cimzia is not known. The impact of long-term treatment with Cimzia on the development of autoimmune diseases is unknown (see Section 4.4 Special Warnings and Precautions for Use).

Laboratory abnormalities
Liver enzyme elevations
In controlled rheumatoid arthritis trials (studies RA-I to RA-IV), when corrected for exposure, the incidence of hepatic enzyme elevations was similar in the subjects receiving placebo as compared to Cimzia (see Section 5 Pharmacological Properties).

Injection site reactions
In the placebo controlled rheumatoid arthritis studies, 5.8% of patients treated with Cimzia developed injection site reactions (erythema, itching, haematoma, pain, swelling or bruising), compared to 4.8% of patients receiving placebo. In particular, injection site pain was observed in 1.5% of patients treated with Cimzia, in the placebo controlled rheumatoid arthritis studies, with no cases leading to withdrawal.

In the placebo controlled psoriasis studies, 3.6% of patients treated with Cimzia developed injection site reactions (reaction, haematoma, pain, erythema, bruising, discolouration, swelling or urticaria), compared to 0.5% of patients receiving placebo. No cases led to discontinuation of study drug.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No case of Cimzia overdose has been reported.

The maximum tolerated dose of Cimzia has not been established. No dose limiting toxicity was observed during clinical trials. Multiple doses of up to 800 mg subcutaneously and 20 mg/kg intravenously have been administered and well tolerated.

In cases of overdosage, it is recommended that patients are monitored closely for any adverse reactions or effect, and appropriate symptomatic treatment initiated immediately.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Certolizumab pegol has a high affinity for human TNFα and binds with a dissociation factor (K_D) of 90 pM. TNFα is a key proinflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralises TNFα (90% inhibitory concentration [IC_{90}]) of 4 ng/mL for inhibition of human TNFα in the *in vitro* L929 murine fibrosarcoma cytotoxicity assay) but does not neutralise lymphotoxin α (TNFβ). Certolizumab pegol cross reacts poorly with TNF from rodents and rabbits, therefore *in vivo* efficacy was evaluated using animal models in which human TNFα was the physiologically active molecule.

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

Certolizumab pegol does not contain a fragment crystallizable (Fc) region, which is normally present in a complete antibody, and therefore does not fix complement or cause antibody dependent cell mediated cytotoxicity *in vitro.* It does not induce apoptosis *in vitro* in human peripheral blood derived monocytes or lymphocytes or 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.

Pharmacodynamic effects
Biological activities ascribed to TNFα include the upregulation of cellular adhesion molecules and chemokines, upregulation of major histocompatibility complex (MHC) class I and class II molecules, and direct leukocyte activation. TNFα stimulates the production of downstream inflammatory mediators, including interleukin-1, prostaglandins, platelet activating factor, and nitric oxide. Elevated levels of TNFα have been implicated in the pathology of rheumatoid arthritis. Increased TNFα levels are found in the synovial fluid of rheumatoid arthritis patients and play an important role in the joint destruction that is a hallmark of this disease.

Clinical trials

Rheumatoid arthritis
The efficacy and safety of Cimzia were assessed in four randomised, 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 disease for at least 6 months prior to baseline. Further inclusion criteria for these trials comprised women being postmenopausal, surgically incapable of child bearing or effectively practicing birth control. Exclusion criteria for these studies were based on medical assessment of conditions covered in Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Adverse Effects (Undesirable Effects) sections. Cimzia was administered subcutaneously in combination with MTX at stable doses of at least 10 mg weekly in

Studies RA-I and RA-II and stable doses of at least 15 mg weekly in Study RA-IV. Cimzia was administered as monotherapy in Study RA-III. There is no experience with Cimzia in combination with DMARDs other than MTX.

Study RA-I and Study RA-II, the pivotal efficacy and safety trials, 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 studies to RA-I and RA-II enrolled 847 and 567 patients respectively, all of whom received 400 mg of Cimzia + MTX every other week for at least 6 months and then 200 mg of Cimzia + MTX every other week. Over the time period of 6.5 years from first subject enrolled to final subject completed in the two pivotal extension studies to RA-I and RA-II, the overall withdrawal rate from the two open label extension studies was approximately 40%. Approximately 16% of the total subjects from each study had subject decision as the reason for withdrawal and for approximately 17%, the reason was an adverse event. For both studies, less than 5% had reasons of lack of efficacy, protocol noncompliance, lost to follow-up or other.

Study RA-III (monotherapy), a supportive efficacy and safety trial, evaluated 220 patients who had failed at least one DMARD prior to receiving Cimzia. Patients were treated with Cimzia 400 mg or placebo every 4 weeks for 24 weeks (the monotherapy maintenance dose of 200 mg every 2 weeks has not been formally evaluated in a clinical trial). Patients were evaluated for signs and symptoms using the ACR20 at Week 24.

Study RA-IV, another supportive efficacy and safety trial, evaluated 247 patients who had active disease despite receiving MTX for at least 6 months prior to study enrolment. Patients received 400 mg of Cimzia every 4 weeks for 24 weeks without a prior loading dose, in combination with MTX. Patients were evaluated for signs and symptoms using the ACR20 at Week 24.

The efficacy and safety of Cimzia was assessed in DMARD naïve adult patients with active RA in a randomized, placebo controlled, double blind clinical trial (C-EARLY). In the C-EARLY trial patients were ≥ 18 years of age and must have been diagnosed with moderate to severe active and progressive RA within 1 year (as defined by the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria). At baseline, 96.9% of subjects in the Cimzia + MTX arm and 95.3% subjects in the PBO + MTX arm had severe RA defined as high disease activity > 5.1. Subjects that had active disease were defined by:

- ≥ 4 swollen and tender joints each (DAS28) at screening and baseline,
- DAS28 (ESR) > 3.2 at screening and baseline,
- CRP ≥ 10 mg/L at screening and/or ESR ≥ 28 mm/h at screening and baseline.

The progressive nature of disease in the study population is indicated by the high disease activity, high swollen joint count (SJC), elevated CRP and ESR, presence of ACPA and/or RA factor. At baseline 77.8% of subjects had erosion, indicating that many subjects already had radiographic progression. Patients had a mean time since diagnosis at baseline of 2.9 months and were DMARD naïve (including MTX). Cimzia was administered subcutaneously in combination with orally administered MTX (no Cimzia monotherapy arm). Patients were treated with a loading dose of 400

mg at Week 0, 2 and 4 or placebo followed by 200 mg of Cimzia or placebo every 2 weeks during 52 weeks. For both the Cimzia and placebo arms, MTX was initiated as of Week 0 (10 mg/week), titrated up to maximum tolerated dose by Week 8 (min 15 mg/week, max 25 mg/week allowed), and maintained throughout the study (average dose of MTX after Week 8 for placebo and Cimzia was 22.3 mg/week and 21.1 mg/week respectively). Patients were evaluated for signs and symptoms using the proportion of subjects in sustained remission at Week 52. Sustained remission is defined as DAS28 [ESR] < 2.6 at both Week 40 and Week 52). Structural damage was also assessed. Subjects were withdrawn at Week 20 if no improvement in disease activity (change in DAS 28 (ESR) ≤ 0) was observed. Subjects were withdrawn at Week 24 if insufficient improvement at Week 20 was confirmed at Week 24 (sufficient improvement in disease activity is defined as: low disease activity (i.e. DAS28 [ESR] ≤ 3.2) and/or, improvement in DAS 28 (ESR) of ≥ 1.2 points since baseline).

Clinical response

The percentage of Cimzia treated patients achieving ACR20, 50, and 70 responses in studies RA-I, RA-II, RA-III and RA-IV are shown in Tables 8 and 9. In studies RA-I and II Cimzia treated patients had statistically significant higher ACR20, 50 and 70 response rates at 6 months compared to placebo treated patients. There was no extra treatment benefit conferred by a dosage regimen of 400 mg every other week compared with 200 mg every other week. The results in Study RA-II (619 patients) were similar to the results in RA-I at Week 24. The results in Study RA-IV (247 patients) were similar to those seen in Study RA-III. Over the one year Study RA-I, 13% of Cimzia + MTX treated patients achieved a major clinical response, defined as achieving an ACR70 response over a continuous 6 month period, compared to 1% of placebo + MTX treated patients.

Table 8: ACR Responses in Studies RA-I and RA-II (Percent of Patients)

Response	Study RA-I Methotrexate Combination (24 and 52 weeks)			Study RA-II Methotrexate Combination (24 weeks)		
	Placebo + MTX N=199	**CIMZIA[(a)] 200 mg q2 weeks + MTX N=393**	**CIMZIA[(a)] 200 mg + MTX - Placebo + MTX (95% CI)[(c)]**	**Placebo + MTX N=127**	**CIMZIA[(a)] 200 mg q2 weeks + MTX N=111**	**CIMZIA[(a)] 200 mg + MTX – Placebo + MTX (95% CI)[(c)]**
ACR20						
Week 24	14%	59%*	45% (38%, 52%)	9%	57%*	49% (41%, 57%)
Week 52	13%	53%*	40% (33%, 47%)	NA	NA	NA
ACR50						
Week 24	8%	37%*	30% (24%, 36%)	3%	33%*	29% (23%, 36%)
Week 52	8%	38%*	30% (24%, 37%)	NA	NA	NA
ACR70						
Week 24	3%	21%*	18% (14%, 23%)	1%	16%**	15% (10%, 20%)
Week 52	4%	21%*	18% (13%, 22%)	NA	NA	NA
Major Clinical Response[(b)]	1%	13%*	12% (8%, 15%)			

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

[(b)] Major clinical response is defined as achieving ACR70 response over a continuous 6-month period.

[(c)] 95% Confidence Intervals constructed using the large sample approximation to the Normal Distribution.

Wald p-values are quoted for the comparison of treatments using logistic regression with factors for treatment and region.

CIMZIA vs. placebo: *p<0.001, **p≤0.01

Table 9: ACR Responses in Studies RA-III and RA-IV

Response	Study RA-III Monotherapy (24 weeks)			Study RA-IV Methotrexate Combination (24 weeks)		
	Placebo N=109	**CIMZIA[a] 400 mg q4 weeks N=111**	**CIMZIA[a] 400 mg - Placebo (95% CI)[b]**	**Placebo + MTX N=119**	**CIMZIA[a] 400mg q4 weeks + MTX N=119**	**CIMZIA[a] 400 mg + MTX – Placebo + MTX (95% CI)[b]**
ACR20 Week 24	9%	46%*	36% (25%, 47%)	23%	46%*	23% (11%, 35%)
ACR50 Week 24	4%	23%*	19% (10%, 28%)	6%	18%**	12% (4%, 20%)
ACR70 Week 24	0%	6%***	6% (1%, 10%)	2%	0%	-2% (-4%, 1%)

[a] CIMZIA administered every 4 weeks not preceded by a loading dose regimen.

[b] 95% Confidence Intervals constructed using the large sample approximation to the Normal Distribution. p-values are derived from the Cochran-Mantel-Haenszel test of treatment comparison stratified by country. CIMZIA vs. placebo: *p<0.001, **p≤0.01, ***p≤0.05

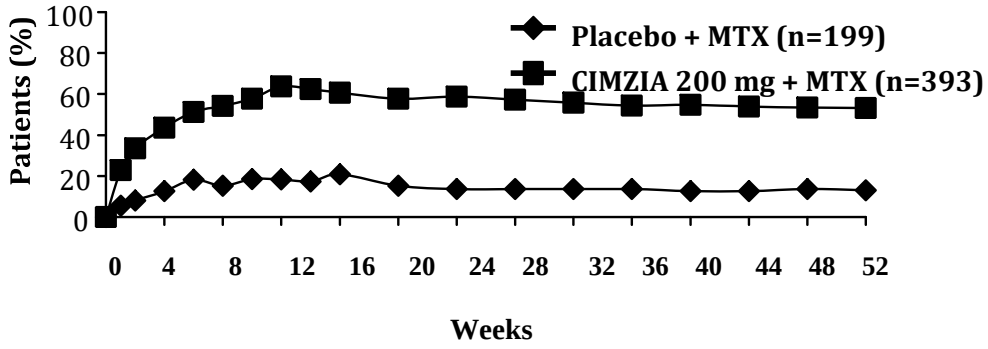
Table 10: Components of ACR Response in Studies RA-I and RA-III

Parameter†	Studies RA-I				Studies RA-III			
	Placebo + MTX N=199		Cimzia[a] 200 mg q2 weeks + MTX N=393		Placebo N=109		CIMZIA[b] 400 mg q4 weeks Monotherapy N=111	
	Baseline	**Week 24**	**Baseline**	**Week 24**	**Baseline**	**Week 24**	**Baseline**	**Week 24**
Number of tender joints (0-68)	28	27	29	9*	28 (12.5)	24 (15.4)	30 (13.7)	16* (15.8)
Number of swollen joints (0-66)	20	19	20	4*	20 (9.3)	16 (12.5)	21 (10.1)	12* (11.2)
Physician global assessment [c]	66	56	65	25*	4 (0.6)	3 (1.0)	4 (0.7)	3* (1.1)
Patient global assessment [c]	67	60	64	32*	3 (0.8)	3 (1.0)	3 (0.8)	3* (1.0)
Pain[c][d]	65	60	65	32*	55 (20.8)	60 (26.7)	58 (21.9)	39* (29.6)
Disability index (HAQ)[e]	1.75	1.63	1.75	1.00*	1.55 (0.65)	1.62 (0.68)	1.43 (0.63)	1.04* (0.74)
CRP (mg/L)	16.0	14.0	16.0	4.0*	11.3	13.5	11.6	6.4*

[a] CIMZIA administered every 2 weeks preceded by a loading dose of 400mg at Weeks 0, 2 and 4.
[b] CIMZIA administered every 4 weeks not preceded by a loading dose regimen.
[c] Study RA-I - Visual Analog Scale: 0 = best, 100 = worst. Study RA-III: Five-Point Scale: 1= best, 5= worst
[d] Patient's Assessment of Arthritis Pain. Visual Analog Scale: 0 = best, 100 = worst
[e] Health Assessment Questionnaire-Disability Index; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.
All values are last observation carried forward. *p<0.001, CIMZIA vs. placebo, based on ANCOVA model with region or country and treatment as factors and baseline as covariate.
†For Study RA-I, the median is presented. For Study RA-III, the mean (SD) is presented except for CRP which is presented as geometric mean.

The percentage of patients achieving ACR20 response by visit for Study RA-I is shown in Figure 1. Among patients receiving Cimzia 200 mg every 2 weeks + MTX, clinical responses were seen in some patients within one (22.9%) to two (33.5%) weeks after initiation of therapy.

Figure 1 Study RA-I ACR20 Response Over 52 Weeks



The safety and efficacy of 400 mg Cimzia administered every 4 weeks in combination with MTX were evaluated Study RA-IV. The primary endpoint of this study was achieved; the proportion of subjects who achieved an ACR20 response at Week 24 was significantly greater in the Cimzia 400 mg + MTX group compared to the placebo + MTX group (45.9% compared to 22.9%, $p < 0.001$).

The C-EARLY trial met its primary and key secondary endpoint. The key results from the study are presented in Table 11.

Table 11: C-EARLY trial: percent of patients in sustained remission, sustained low disease activity and with ACR50 at Week 52

Response	Placebo + MTX N=213	CIMZIA 200mg + MTX N = 655
Sustained remission[a] (DAS28(ESR) <2.6 at both Week 40 and Week 52)	15.0%	28.9%[b]
Sustained low disease activity (DAS28(ESR) ≤3.2 at both Week 40 and Week 52)	28.6%	43.8%[b]
ACR 50	52.6%	61.8%[c]

[a] Primary endpoint of C-EARLY trial (to Week 52).
Full analysis set, non-responder imputation for missing values.
[b] p<0.001
[c] p<0.05
CIMZIA+MTX vs placebo+MTX: p value was estimated from a logistic regression model with factors for treatment, region, and time since rheumatoid arthritis diagnosis at Baseline (≤4 months vs >4 months)

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 + MTX inhibited the progression of structural damage compared to placebo plus MTX after 12 months of treatment as shown in Table 12. In the Cimzia 200 mg every other week + MTX treatment group, 69% of patients experienced no radiographic progression (mTSS ≤ 0.0), compared to 52% of patients in the placebo group. Study RA-II showed similar results to RA-I at Week 24.

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

	Placebo + MTX Mean (SD)		**CIMZIA[(a)] 200 mg q2 weeks + MTX Mean (SD)**		**CIMZIA[(a)] 200 mg + MTX – Placebo + MTX Mean Difference**	
	RA-I N=199	**RA-II N=127**	**RA-I N=393**	**RA-II N= 246**	**RA-I N=199**	**RA-II N=127**
mTSS						
N	199	125	391	241	--	--
Baseline	39 (45)	47 (59)	38 (49)	40 (50)	--	--
N	180	112	353	214	--	--
Week 24	1.3 (3.8)	1.2 (4.1)	0.2 (3.2)	0.2 (2.7)	-1.1	-1.0
N	181	N/A	364	N/A		
Week 52	2.8 (7.8)	N/A	0.4 (5.7)	N/A	-2.4	N/A
Erosion Score[(b)]						
Baseline	14 (21)	23 (32)	15 (24)	19 (27)	--	--
Week 24	0.7 (2.1)	0.7 (2.6)	0.0 (1.5)	0.1 (2.0)	-0.7	-0.6
Week 52	1.5 (4.3)	N/A	0.1 (2.5)	N/A	-1.4	N/A
JSN Score[(b)]						
Baseline	25 (27)	23 (28)	24 (28)	21 (24)	--	--
Week 24	0.7 (2.4)	0.5 (2.3)	0.2 (2.5)	0.1 (1.4)	-0.5	-0.4
Week 52	1.4 (5.0)	N/A	0.4 (4.2)	N/A	-1.0	N/A

CIMZIA+MTX vs placebo+MTX: p value was estimated from a logistic regression model with factors for treatment, region, and time since rheumatoid arthritis diagnosis at Baseline (≤4 months vs >4 months)

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

For RA-I, p-values were < 0.001 at Week 24 and 52 for both mTSS and erosion score and ≤ 0.01 at both time points for JSN. For RA-II, p-values were ≤0.01at Week 24 for mTSS, erosion score and JSN score.
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.

[(b)] n values for erosion score and JSN score are the same as for mTSS.

Of the 783 patients initially randomized to active treatment in RA-I, 508 completed 52 weeks of placebo controlled treatment and entered the open label extension study. Sustained inhibition of progression of structural damage was demonstrated in a subset of 449 of these patients who completed at least 2 years of treatment with Cimzia (RA-I and open label extension study) and had evaluable data at the 2 year timepoint. This was not a preplanned analysis. Linear imputation was used for missing data. There were 177 patients in the control group, including 136 withdrawers (subjects who received placebo + MTX for 12 weeks and failed to achieve an ACR20 response at Week 12, confirmed at Week 14 who then participated in the open label extension study from Week 16) and 41 completers (subjects who received placebo + MTX for 52 weeks before participating in the open label extension study). The efficacy of Cimzia on radiographic endpoints has not been established in patients who are unable to tolerate MTX therapy.

In C-EARLY, at Week 52, the mean changes (SD) from baseline in mTSS were:

- 0.2 (3.2) in the Cimzia + MTX group and
- 1.8 (4.3) in the PBO + MTX group

The Cimzia + MTX - PBO + MTX treatment difference was -0.978 (-1.005, -0.500) (Hodges-Lehmann point estimate of shift and 95% asymptotic (Moses) confidence interval). A p-value of < 0.001 for the treatment difference was estimated from an ANCOVA model on the ranks with treatment, region, time since RA diagnosis at baseline (≤ 4 months vs > 4 months) as factors and baseline rank as covariate.

Physical function response and health related outcomes

In studies RA-I, RA-II, RA-III and RA-IV, Cimzia treated patients reported significant improvements in physical function as assessed by the Health Assessment Questionnaire - Disability Index (HAQ-DI) and in tiredness (fatigue) as reported by the Fatigue Assessment Scale (FAS) from Week 1 through to the end of the studies compared to placebo. In all clinical trials, Cimzia treated patients reported significantly greater improvements in the SF-36 Physical and Mental Component Summaries and all domain scores. Improvements in physical function and HRQoL were maintained through 2 years in the open label extension to RA-I. In studies RA-I and RA-II, Cimzia treated patients reported statistically significant improvements in the Work Productivity Survey compared to placebo.

In C-EARLY, at Week 52, subjects in the CZP + MTX group had a statistically significant improvement in physical functioning over the PBO + MTX group (-1.0 vs -0.82 points; $p < 0.001$), as assessed in the change from baseline in HAQ-DI.

Psoriatic arthritis

The efficacy and safety of Cimzia were assessed in a multicentre, randomized, double blind, placebo controlled clinical trial (PsA001) in 409 patients ≥ 18 years of age with adult onset active psoriatic arthritis for at least 6 months as defined by the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria. Patients had ≥ 3 swollen and tender joints and increased acute phase reactants. Patients also had active psoriatic skin lesions or a documented history of psoriasis and had failed 1 or more DMARDs. Previous treatment with one TNF-antagonist was allowed and 20% of patients had prior TNF-antagonist exposure. 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 2 weeks or 400 mg every 4 weeks or placebo every 2 weeks. Patients receiving concomitant NSAIDs and conventional DMARDs were 72.6% and 70.2 % respectively. The two primary endpoints were the percentage of patients achieving ACR20 response at Week 12 and change from baseline in modified Total Sharp Score (mTSS) at Week 24.

ACR response

The percentage of Cimzia treated patients achieving ACR20, 50 and 70 responses in the PsA001 clinical trial are shown in Table 13. Cimzia treated patients had a statistically significant higher ACR20 response rate at Week 12 and Week 24 compared with placebo treated patients ($p < 0.001$). Cimzia treated patients also had significant improvements in ACR50 and 70 response rates and for each ACR component at Week 12 and 24 compared to placebo (see Table 14). Responses were similar in patients receiving Cimzia 200 mg every 2 weeks or Cimzia 400 mg every 4 weeks.

Table 13: Key efficacy outcomes in PsA001 clinical trial (percent of patients)

Response	**Placebo N=136**	**CIMZIA[(a)]200 mg Q2W N=138**	**CIMZIA[(b)] 400 mg Q4W N=135**
ACR20			
Week 12	24%	58%**	52%**
Week 24	24%	64%**	56%**
ACR50			
Week 12	11%	36%**	33%**
Week 24	13%	44%**	40%**
ACR70			
Week 12	3%	25%**	13%*
Week 24	4%	28%**	24%**
Response	**Placebo N=86**	**CIMZIA[(a)]200 mg Q2W N=90**	**CIMZIA[(b)] 400 mg Q4W N=76**
PASI 75			
Week 12	14%	47%**	47%**
Week 24	15%	62%**	61%**
PASI 90			
Week 12	5%	22%**	20%*
Week 24	6%	47%**	36%**

N reflects number of randomised patients; number for PASI is based on the subset of patients with ≥ 3% body surface area (BSA) involvement at baseline.

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

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

**p<0.001, CIMZIA vs placebo

*p<0.01, CIMZIA vs placebo

Results are from the randomized set. Treatment Difference: CIMZIA 200 mg-placebo, CIMZIA 400 mg –placebo (and corresponding 95% CI and p-value) are estimated using a standard two-sided Wald asymptotic standard errors. Non-responder Imputation (NRI) is used.

Table 14: Components of ACR response in PsA001 clinical trial

Parameter	**Placebo N=136**			**CIMZIA[(a)] 200 mg Q2W N=138**			**CIMZIA[(b)] 400 mg Q4W N=135**		
	Baseline	**Week 12**	**Week 24**	**Baseline**	**Week 12**	**Week 24**	**Baseline**	**Week 12**	**Week 24**
Number of tender joints (0-68)[(c)]	19.9	16.5	17.0	21.5	11.2*	8.5*	19.6	11.2*	9.4*
Number of swollen joints (0-66)[(c)]	10.4	8.7	9.9	11.0	4.0*	3.1*	10.5	4.7*	3.0*
Physician Global	58.7	44.1	42.2	56.8	24.8*	19.6*	58.2	28.7*	21.1*

assessment[c, d]									
Patient global assessment[c, d]	57.0	50.2	49.0	60.2	32.6*	31.1*	60.2	39.6*	32.5*
Pain[c, e]	60.0	50.2	48.8	59.7	32.8*	31.1*	61.1	38.6*	32.7*
Disability index (HAQ)[c, f]	1.30	1.15	1.13	1.33	0.87*	0.81*	1.29	0.90*	0.86*
CRP (mg/L)	18.56	14.75	14.66	15.36	5.67*	4.58*	13.71	6.34*	7.37*

[a] CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4.
[b] CIMZIA administered every 4 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4.
[c] Last Observation Carried Forward is used for missing data, early withdrawals or placebo escape.
[d] Patient and Physician Global Assessment of Disease Activity, VAS 0= best 100= worst
[e] The Patient Assessment of Arthritis Pain, VAS 0= no pain and 100= most severe pain
[f] 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). *p<0.001, CIMZIA vs placebo

The percentage of ACR20 responders was clinically relevant and significantly higher for the Cimzia 200 mg every 2 weeks and Cimzia 400 mg every 4 weeks treatment groups compared to placebo group at every visit after baseline through week 24 ($p \leq 0.001$ at each visit).

Patients with enthesitis and dactylitis at baseline were evaluated for mean improvement in Leeds Enthesitis Index (LEI) and Leeds Dactylitis Index (LDI). Cimzia treated patients either 200 mg every 2 weeks or 400 mg every 4 weeks showed greater reduction in enthesitis (-1.8; -1.7) as compared with placebo treated patients (-0.9) at Week 12 ($p < 0.001$ and $p < 0.01$, respectively) and Week 24 (200 mg every 2 weeks: -2.0; 400 mg every 4 weeks: 1.8; placebo: -1.1) ($p < 0.001$; $p < 0.01$, respectively). Also, the same dose regimens showed greater reduction in dactylitis (mean change from baseline -30.40; -45.46) as compared with placebo treated patients (-16.79) at Week 12 ($p < 0.05$ and $p < 0.001$, respectively) and Week 24 (200 mg every 2 weeks: -40.69; 400 mg every 4 weeks: -53.47, placebo: -22.04) ($p < 0.01$; $p < 0.001$, respectively).

Radiographic response
In PsA001 clinical trial, 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 joints. Radiographic data for baseline or Week 24 were missing for 12% of randomized subjects; analysis was conducted using *post hoc* imputation rules with a minimum of an 8 week time window between X-rays applied. Cimzia treatment reduced the radiographic progression compared with placebo treatment at Week 24 as measured by change from baseline in total mTSS score (LS mean [± SE] score was 0.28 [± 0.07] in the placebo group compared with 0.06 [± 0.06] in the Cimzia all doses group; $p = 0.007$).

Physical function response and health related outcomes
In PsA001 clinical trial, Cimzia treated patients reported significant improvements in physical function as assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI) and in pain as assessed by the Patient Assessment of Arthritis Pain (PAAP) from Week 1 through Week 24 as compared to placebo (see Table 14). Cimzia treated patients reported significant improvements in tiredness (fatigue) as reported by the Fatigue Assessment Scale (FAS) from Week 2 through Week 24 as compared to placebo. Cimzia treated patients reported significant improvements in health related quality of life as measured by the psoriatic arthritis QoL (PsAQoL) and the SF-36 Physical and

Mental Component Summaries in all domain scores from Week 4 through Week 24. Cimzia treated patients reported improvements in psoriatic arthritis related productivity at work and within household, as reported by the Work Productivity Survey from Week 4 through Week 24 compared to placebo.

Non-radiographic axial spondyloarthritis and ankylosing spondylitis

AS001 (ankylosing spondylitis)

The efficacy and safety of Cimzia were assessed in one multicentre, randomized, double blind, placebo controlled trial (AS001) in 325 patients ≥ 18 years of age with adult onset active axial spondyloarthritis for at least 3 months as defined by the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial spondyloarthritis. Axial spondyloarthritis refers to spondyloarthritis with predominantly axial involvement and includes the disease subgroup of patients with definitive signs of damage suggestive as consequence of sacroiliitis on X-ray (ankylosing spondylitis), as well as a disease subgroup with no definitive evidence of sacroiliitis on plain radiographs (nonradiographic axial spondyloarthritis). Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4, spinal pain ≥ 4 on a 0 to 10 numerical rating scale (NRS) and increased CRP or current evidence of sacroiliitis on magnetic resonance imaging (MRI). Patients must have been intolerant to or had an inadequate response to at least one NSAID.

Overall 20.2% of AS patients had prior TNF-antagonist exposure. Patients were treated with a loading dose of Cimzia 400 mg at Weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either 200 mg of Cimzia every 2 weeks or 400 mg of Cimzia every 4 weeks or placebo. 91% of AS patients received concomitant NSAIDs.The primary efficacy endpoint was the ASAS20 response rate at Week 12. One hundred and seventy eight patients (54.8%) patients in the study had active AS, and only these results are presented.

ASAS response

In AS001 clinical trial, at Week 12 ASAS20 responses were achieved by 57% of patients receiving Cimzia 200 mg every 2 weeks and 64% of patients receiving Cimzia 400 mg every 4 weeks as compared to 37% of patients receiving placebo ($p < 0.01$). At Weeks 12 and 24, the percentage of subjects with an ASAS40 response was greater in the Cimzia treated groups compared to placebo. Responses were similar in AS patients receiving Cimzia 200 mg every 2 weeks or Cimzia 400 mg every 4 weeks (see Table 15).

Cimzia treated patients also had significant improvement compared to placebo in multiple components of ankylosing spondylitis disease activity (see Table 16).

Table 15: Efficacy response in AS001 clinical trial: reduction of signs and symptoms in ankylosing spondylitis sub-populations (percent of patients)

Parameters	**Ankylosing spondylitis**			
	Placebo N=57	**CIMZIA 200 mg every 2 weeks N=65**	**CIMZIA 400 mg every 4 weeks N=56**	**CIMZIA all dosing regimens[a] N=121**
ASAS20[b,c]				
Week 12	37%	57%*	64%*	60%*
Week 24	33%	68%**	70%**	69%**
ASAS40[c,d]				

Week 12	19%	40%*	50%**	45%**
Week 24	16%	48%**	59%**	53%**
ASAS 5/6[c,d]				
Week 12	9%	48%**	36%**	42%**
Week 24	5%	34%**	46%**	40%**
Partial remission[c,d]				
Week 12	2%	20%**	20%*	20%**
Week 24	7%	31%**	25%*	28%**
BASDAI 50 [c,d]				
Week 12	11%	42%**	41%**	41%**
Week 24	16%	43%**	55%**	49%**

[a] CIMZIA all dosing regimen = data from CIMZIA 200 mg administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4 plus CIMZIA 400 mg administered every 4 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4.
[b] Results are from the randomized set.
[c] Treatment difference: CIMZIA 200-placebo, CIMZIA 400-placebo (and corresponding 95% CI and p-value) are estimated using a standard two-sided Wald asymptotic test. Non-responder imputation (NRI) is used.
[d] Full Analysis Set.
NA = not available
*p≤ 0.05, CIMZIA vs placebo
**p<0.001, CIMZIA vs placebo

Table 16: Components of the ASAS response criteria and other measures of disease activity in AS patients at baseline and Week 12 in study AS001

	Placebo N=57		**CIMZIA[a] 200mg Every 2 weeks N=65**		**CIMZIA[b] 400mg every 4 weeks N=56**	
ASAS response criteria	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
-Patient Global Assessment (0-10)	6.9	5.6	7.3	4.2	6.8	3.8
-Total spinal pain (0-10)	7.3	5.8	7.0	4.3	6.9	4.0
-BASFI (0-10)[c]	6.0	5.2	5.6	3.8	5.7	3.8
-Inflammation (0-10)	6.7	5.5	6.7	3.8	6.4	3.4
BASDAI (0-10)[d]	6.4	5.4	6.5	3.9	6.2	3.7
BASMI [e]	4.7	4.4	4.2	3.6	4.3	3.9

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

In the AS subpopulation, the percentage of ASAS20 responders was clinically relevant and significantly higher for the Cimzia 200 mg every 2 weeks and Cimzia 400 mg every 4 weeks treatment groups compared to placebo group at every visit after baseline through Week 24 ($p < 0.05$ at each visit).

Spinal mobility
Spinal mobility was assessed by BASMI. The difference to placebo in mean change from baseline in BASMI linear at Week 24 was -0.32 points ($p < 0.05$) in Cimzia treated patients.

Maastricht Ankylosis Spondylitis Enthesitis Score (MASES)
The assessment of enthesitis showed a clinically meaningful improvement ($p < 0.001$) in Cimzia

treated patients compared with placebo treated patients at Week 24.

Inhibition of inflammation in magnetic resonance imaging (MRI)
In an imaging substudy signs of inflammation were assessed by MRI at Week 12 and expressed as change from baseline in SPARCC (Spondyloarthritis Research Consortium of Canada) score for sacroiliac joints and ASspiMR - a score in the Berlin modifications for the spine. Significant inhibition of inflammatory signs in both sacroiliac joints and the spine was observed in the Cimzia treated patient (all doses group), in the subpopulation of ankylosing spondylitis patients, but not in placebo treated patients.

Physical function response and health related outcomes
In AS001 clinical trial, Cimzia treated AS patients reported significant improvements in physical function as assessed by the BASFI and in pain as assessed by the nocturnal back pain NRS scales from Week 1 through Week 24 as compared to placebo. Cimzia treated AS patients reported significant improvements in tiredness (fatigue) as reported by the BASDAI fatigue item from Week 1 through Week 24 as compared to placebo (see Table 16). Cimzia treated patients reported significant improvements in health related quality of life as measured by the ankylosing spondylitis QOL (ASQoL) at Week 24.

AS0005 (non-radiographic axial spondyloarthritis and ankylosing spondylitis)
The efficacy and safety of dose reduction and treatment withdrawal in patients in sustained remission were assessed in adult patients (18-45 years of age) with early active axSpA (symptom duration of less than 5 years), an ASDAS score ≥2.1 (and similar disease inclusion criteria as in the AS001 study), and who had inadequate response to at least 2 NSAIDs or an intolerance to or contraindication for NSAIDs. Patients included both the AS and nr-axSpA subpopulations of axSpA, and were enrolled into an open-label run-in 48-Week period (Part A) during which they all received 3 loading doses of Cimzia 400 mg at Weeks 0, 2, and 4 followed by Cimzia 200 mg every 2 weeks from Week 6 to Week 46.
Patients who achieved sustained remission (defined as having inactive disease (ASDAS<1.3) over a period of at least 12 weeks) and remained in remission at week 48, were randomized into Part B and received either Cimzia 200 mg every 2 weeks (N=104), Cimzia 200 mg every 4 weeks (dose reduction, N=105), or placebo (treatment withdrawal, N=104) for 48 Weeks.
The primary efficacy variable was the percentage of patients who did not experience a flare during Part B.
Patients who experienced a flare in Part B, ie, had an ASDAS ≥2.1 at 2 consecutive visits or ASDAS >3.5 at any visit during Part B, received escape treatment of Cimzia 200 mg every 2 weeks for at least 12 weeks (with a loading dose of Cimzia 400 mg at Week 0, 2 and 4 in placebo-treated patients).

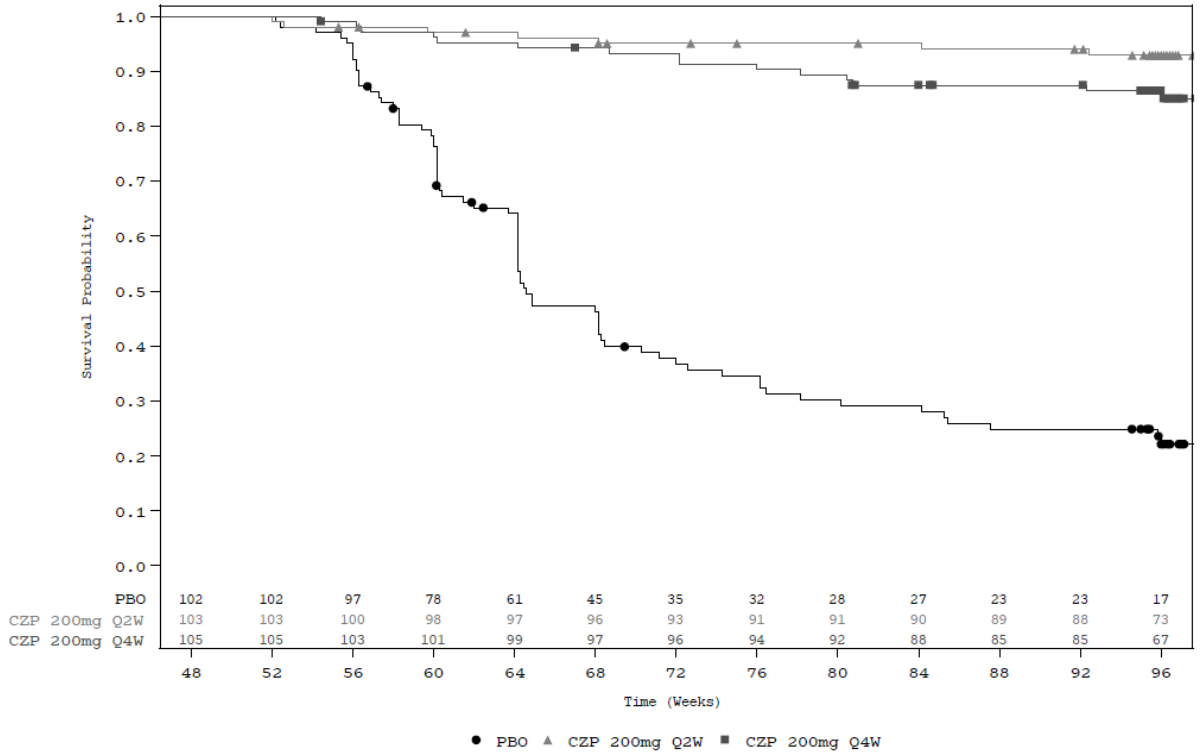
Clinical response

The percentage of patients who achieved sustained remission at Week 48 in Part A was 43.9% for the overall axSpA population, and was similar in the nr-axSpA (45.3%) and AS (42.8%) subpopulations.

Among the patients who were randomized in Part B (N = 313), a statistically significant ($p < 0.001$, NRI) greater proportion of patients did not experience a flare when continuing treatment with Cimzia 200 mg every 2 weeks (83.7%) or CIMZIA 200 mg every 4 weeks (79.0%) compared with treatment withdrawal (20.2%).

The difference in time to flare between the treatment withdrawal group and either of the Cimzia treatment groups, was clinically meaningful (nominal $p<0.001$ for each comparison). In the placebo group, flares started approximatively 8 weeks after Cimzia was withdrawn, with the majority of flares occurring within 24 weeks of treatment withdrawal (Figure 2).

Figure 2: Kaplan-Meier curve of time to flare



Non responder imputation (NRI) was used; Results are for the Randomized Set
Note: Time to flare was defined as the time from the date of randomization to the date of the flare. For study participants who did not have a flare, the time to flare was censored at the date of Week 96 Visit.
The Kaplan-Meier plot was truncated to 97 weeks when <5% of participants were still remaining in the study.
The numbers within frame at bottom represent the number of subjects at risk per treatment group at the start of each 4 week period.
The symbols represent a censored subject(s).

Results for Part B are presented in Table 17 and 18.

Table 17 Summary of study participants who did not experience a flare in Part B (NRI, RS)

	PBO (CZP Withdrawal) N=104	**CZP 200mg Q2W N=104**	**CZP 200mg Q4W N=105**
Study participants with flare, n (%)	83 (79.8)	17 (16.3)	22 (21.0)
Study participants with no flare, n (%) (95% CI)	21 (20.2) (13.0, 29.2)	87 (83.7) (75.1, 90.2)	83 (79.0) (70.0, 86.4)
Odds ratio versus PBO (95% CI)	-	18.822 (9.605, 38.864)	14.069 (7.395, 27.955)
p-value	-	<0.001	<0.001

CI=confidence interval; CZP=certolizumab pegol; NRI=nonresponder imputation; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set.

Table 18 Maintenance of clinical response in Part B at Week 96

Endpoints	Placebo (treatment withdrawal) N=104	CIMZIA 200 mg every 2 weeks N=104	CIMZIA 200 mg every 4 weeks N=105
ASDAS-MI, n (%)[1]			
Part B Baseline (Week 48)	84 (80.8)	90 (86.5)	89 (84.8)
Week 96	11 (10.6)	70 (67.3)*	61 (58.1)*
ASAS40, n (%)[1]			
Part B Baseline (Week 48)	101 (97.1)	103 (99.0)	101 (96.2)
Week 96	22 (21.2)	88 (84.6)*	77 (73.3)*
BASDAI change from Part B baseline (Week 48), LS mean (SE)[2]			
Week 96	3.02 (0.226)	0.56 (0.176)*	0.78 (0.176)*
ASDAS change from Part B baseline (Week 48), LS mean (SE)[2]			
Week 96	1.66 (0.110)	0.24 (0.077)*	0.45 (0.077)*

[1] Non responder imputation (NRI) was used; Results are for the Randomized Set
[2] mixed model with repeated measures (MMRM) was used; Results are for the Randomized Set
ASDAS-MI = Ankylosing Spondylitis Disease Activity Score-Major Improvement; ASAS: Assessment of Sponyloarthritis international Society; ASAS40= ASAS40% response criteria; SE = Standard error;
Note: ASDAS major improvement is defined as a reduction from Baseline ≥2.0.
Note: Part A Baseline was used as a reference to define ASDAS clinical improvement variables and ASAS variables
* Nominal p<0.001, CIMZIA vs. placebo

Inhibition of inflammation in Magnetic Resonance imaging (MRI)

In Part B, signs of inflammation were assessed by MRI at Week 48 and at Week 96 and expressed as change from baseline in SIJ SPARCC and ASspiMRI-a score in the Berlin modifications. Patients who were in sustained remission at Week 48 had no or very low inflammation, and no meaningful increase in inflammation was observed at Week 96 irrespective of their treatment group.

Retreatment in patients that experience a flare

In Part B, 70% (73/104) placebo-treated patients, 14% (15/105) patients treated with Cimzia 200 mg every 4 weeks and 6.7% (7/104) patients treated with Cimzia 200 mg every 2 weeks experienced a flare and were subsequently treated with Cimzia 200 mg every 2 weeks.

Among the 15 patients who flared in the group allocated to Cimzia 200 mg every 4 weeks, all patients completed 12 weeks of rescue therapy with Cimzia and had available ASDAS data, out of which 12 (80%) had ASDAS Low or Inactive disease (i.e. all ASDAS <2.1) after 12 weeks of restarting the open-label treatment.

Among the 73 patients who flared in the group allocated to treatment withdrawal, 71 completed 12 weeks of rescue therapy with Cimzia, out of which 64 (90%) had ASDAS Low or Inactive disease (i.e. all ASDAS < 2.1) after 12 weeks of restarting the open-label treatment. The number of patients who flared in the 2 Cimzia groups in this trial was too small to make valid assessment of the impact of re-treatment in those cases.

Based on the results from AS0005, a dose reduction in patients in sustained remission after one year of treatment with Cimzia may be considered (See Section 4.2 Dose and Method of Administration).

AS0006 (non-radiographic axial spondyloarthritis)

The efficacy and safety of Cimzia were assessed in a 52 week multicenter, randomized, double-blind, placebo-controlled study (AS0006) in 317 subjects ≥18 years of age with adult-onset active axial spondyloarthritis and back pain for at least 12 months. Patients had to fulfil ASAS criteria for nr-axSpA (not including family history and good response to NSAIDs), and have had objective signs of inflammation indicated by C-reactive protein (CRP) levels above the upper limit of normal and/or sacroiliitis on magnetic resonance imaging (MRI), indicative of inflammatory disease [positive CRP (> ULN) and/or positive MRI], but without definitive radiographic evidence of structural damage on sacroiliac joints.

Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and spinal pain ≥4 on a 0 to 10 Numerical Rating Scale (NRS). Patients must have been intolerant to or had an inadequate response to at least two NSAIDs. Patients were treated with a loading dose of Cimzia 400 mg at Weeks 0, 2 and 4 or placebo followed by 200 mg of Cimzia every 2 weeks or placebo. Utilization and dose adjustment of concomitant medications (including NSAIDs, DMARDs, corticosteroids, opioids) were permitted at any time. Patients were allowed to transition to use of open-label CIMZIA at any time at the discretion of the investigator. However, no patients transitioned before Week 12. The primary endpoint was the proportion of subjects achieving an ASAS40 response at Week 12. The key secondary endpoints included ASDAS-MI response at Week 52, ASAS40 response at Week 52, and change from baseline in BASDAI and BASFI at weeks 12 and 52. ASDAS-MI response was defined as an ASDAS reduction (improvement) ≥ 2.0 relative to baseline or as reaching the lowest possible score.

At baseline, 37 % and 41% of patients had high disease activity (ASDAS ≥2.1, ≤3.5), 62% and 58% of patients had very high disease activity (ASDAS >3.5) and the mean BASDAI score was 6.88 and 6.79 in the CIMZIA group and placebo group respectively.

In study AS0006, at Week 12, statistically significant and clinically meaningful differences in ASAS40 response were observed in patients treated with CIMZIA compared to patients treated with placebo. At Week 52, a greater proportion of nr-axSpA patients treated with CIMZIA achieved ASDAS-MI response compared to patients treated with placebo (Table 19).

Table 19: Clinical Responses in nr-axSpA patients at week 12 and 52 in study AS0006

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

[(a)]CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
All percentages reflect the proportion of patients who responded in the full analysis set.
*p<0.001, CIMZIA vs placebo

The results of the components of the ASAS40 response criteria are shown in Table 20.

Table 20: Components of the ASAS40 and ASDAS-MI response criteria, and other measures of disease activity in nr-axSpA subjects; at baseline and at Weeks 12 in study AS0006

	Placebo N=158		**CIMZIA[a] 200 mg every 2 weeks N=159**	
	Baseline	Week 12	Baseline	Week 12
ASAS40 response criteria				
Total spinal pain	6.9	6.1	7.0	4.0
Patient Global Assessment of Disease Activity[b]	6.7	5.9	6.8	3.9
Inflammation[c]	6.70	5.49	6.92	3.58
Function (BASFI)	5.44	4.95	5.41	3.20
ASDAS-MI response criteria[d]				
Back pain	7.4	6.2	7.4	4.2
Peripheral pain and swelling	6.2	5.3	6.3	3.7
CRP (mg/L)	15.84	14.58	15.79	6.62
BASDAI	6.79	5.71	6.88	3.93
BASMI	2.80	2.75	2.96	2.55

(a) CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
(b) Also a component of ASDAS-MI
(c) The average of BASDAI question 5 and 6 concerning morning stiffness intensity and duration
(d) ASDAS-MI criteria not already listed as part of ASAS40
Note: Last observation carried forward was used for each component

Signs of inflammation were assessed by MRI at Week 12 and expressed as change from baseline in SPARCC (Spondyloarthritis Research Consortium of Canada) score for sacroiliac joints. At Week 12, significant inhibition of inflammation in sacroiliac joints was demonstrated by a reduction of inflammation in Cimzia-treated patients (-4.3) vs placebo-treated patients (0.3) as compared to baseline. Patients treated with Cimzia achieved a greater reduction in nocturnal spinal pain (NRS) compared to placebo-treated patients (reduction compared to baseline -4.0 vs -2.1) at Week 52.

Other Health Related Outcomes
In Study AS0006, patients treated with Cimzia achieved significantly greater improvement from baseline in the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score compared to placebo-treated patients at Week 52.

Plaque psoriasis
The efficacy and safety of Cimzia were assessed in two placebo-controlled studies (CIMPASI-1 and CIMPASI-2) and one placebo-and active-controlled study (CIMPACT) in patients ≥18 years of age with moderate to severe chronic plaque psoriasis for at least 6 months. Patients had a Psoriasis Area and Severity Index (PASI) score ≥ 12, body surface area (BSA) involvement of ≥ 10%, Physician Global Assessment (PGA) of ≥ 3, and were candidates for systemic therapy and / or phototherapy and/or chemophototherapy. Patients who were 'primary' non-responders on any prior biologic therapy (defined as no response within the first 12 weeks of treatment) were excluded from the phase III studies. Patients were predominantly men (64%) and Caucasian (94%), with a mean age of 45.7 years (18 to 80 years); of these, 7.2% were ≥ 65 years of age. The efficacy and safety of Cimzia were evaluated versus Enbrel in the CIMPACT study. In studies CIMPASI-1 and CIMPASI-2 the co-primary efficacy endpoints were the proportion of patients achieving PASI 75 and PGA "clear" or "almost clear" (with at least a 2-point reduction from baseline) at Week 16. In the CIMPACT study, the primary efficacy endpoint was the proportion of patients achieving PASI 75 at Week 12. PASI75 and PGA at Week 16 were key secondary endpoints. PASI 90 at Week 16 was a key secondary endpoint in all 3 studies.

CIMPASI-1 and CIMPASI-2 evaluated 234 patients and 227 patients respectively. In both studies patients were randomized to receive placebo or Cimzia 200 mg every 2 weeks (following a loading dose of Cimzia 400 mg at Weeks 0, 2 and 4) or Cimzia 400 mg every 2 weeks. At week 16, patients randomized to Cimzia who achieved a PASI 50 response continued to receive Cimzia up to Week 48 at the same randomized dose. Patients originally randomized to placebo that achieved a PASI 50 response but not a PASI 75 response at Week 16 received Cimzia 200 mg every 2 weeks (with a loading dose of Cimzia 400 mg at Weeks 16, 18, and 20). Patients with an inadequate response at Week 16 (PASI 50 non-responders) were eligible to receive Cimzia 400 mg every 2 weeks in an open label manner for a maximum of 128 weeks.

The CIMPACT study evaluated 559 patients. Patients were randomized to receive placebo, or Cimzia 200 mg every 2 weeks (following a loading dose of Cimzia 400 mg at Weeks 0, 2 and 4), or Cimzia 400 mg every 2 weeks up to Week 16, or Enbrel 50 mg twice weekly, up to Week 12. Patients originally randomized to Cimzia who achieved a PASI75 response at Week 16 were re-randomized based on their original dosing schedule. Patients on Cimzia 200 mg every 2 weeks were re-randomized to Cimzia 200 mg every 2 weeks, Cimzia 400 mg every 4 weeks or placebo. Patients on Cimzia 400 mg every 2 weeks were re-randomized to Cimzia 400 mg every 2 weeks, Cimzia 200 mg every 2 weeks, or placebo. Patients were evaluated in a double-blind placebo-controlled manner through Week 48. All patients who did not achieve a PASI 75 response at Week 16 entered an escape arm and received Cimzia 400 mg every 2 weeks in an open label manner for a maximum of 128 weeks.

In all three studies, the 48-week maintenance period was followed by a 96-week open label treatment period for the patients who were PASI 50 responders at Week 48. All patients on blinded treatment started the open-label period at Cimzia 200 mg every two weeks. During the open-label treatment period dose changes between Cimzia 200 mg every two weeks and Cimzia 400 mg every two weeks were allowed on the basis of lack of a PASI 50 response or at the discretion of the study investigator. The maximum duration of the studies was 144 weeks.

Of the 850 patients randomized to receive placebo or Cimzia in these placebo-controlled studies, 29% of patients were naïve to prior systemic therapy for the treatment of psoriasis. 47% had received prior phototherapy or chemophototherapy, and 30% had received prior biologic therapy for the treatment of psoriasis. Of the 850 patients, 14% had received at least one TNF-antagonist, 13% had received an anti-IL-17, and 5% had received an anti-IL 12/ 23. Eighteen percent of patients reported a history of psoriatic arthritis at baseline. The mean PASI score at baseline was 20 and ranged from 12 to 69. The baseline PGA score ranged from moderate (70%) to severe (30%). Mean baseline BSA was 25% and ranged from 10% to 96%.

Clinical response at Week 16 and 48

The key results of CIMPASI-1 and CIMPASI-2 studies are presented in Table 21.

Table 21: Clinical response in studies CIMPASI-1 and CIMPASI-2 at Week 16 and Week 48

	Week 16			**Week 48**	
CIMPASI-1					
	Placebo N=51	CIMZIA[a)] 200 mg Q2W N=95	CIMZIA 400 mg Q2W N=88	CIMZIA 200 mg Q2W N=95	CIMZIA 400 mg Q2W N=88
PGA clear or almost clear[b)]	4.2%	47.0%*	57.9%*	52.7%	69.5%
PASI 75	6.5%	66.5%*	75.8%*	67.2%	87.1%
PASI 90	0.4%	35.8%*	43.6%*	42.8%	60.2%
Change from baseline in DLQI, mean +_SD	-3.3 (6.9)	-8.9 (8.5)*	-9.6 (6.5)*	-8.8 (8.5)	-9.8 (7.4)
CIMPASI-2					
	Placebo N=49	CIMZIA [a)] 200 mg Q2W N=91	CIMZIA 400 mg Q2W N=87	CIMZIA 200 mg Q2W N= 91	CIMZIA 400 mg Q2W N= 87
PGA clear or almost clear[b)]	2.0%	66.8%*	71.6%*	72.6%	66.6%
PASI 75	11.6%	81.4%*	82.6%*	78.7%	81.3%
PASI 90	4.5%	52.6%*	55.4%*	59.6%	62.0%
Change from baseline in DLQI, mean (SD)	-2.9 (6.6)	-11.1 (7.8)*	-10.0 (7.6)*	-10.7 (8.3)	-10.9 (7.5)

[a)] CIMZIA 200 mg administered every 2 weeks preceded by a loading dose of 400 mg at Week 0, 2, 4.

[b)] PGA 5 category scale. Treatment success of "clear" (0) or "almost clear"(1) consisted of no signs of psoriasis or normal to pink coloration of lesions, no thickening of the plaque, and none to minimal focal scaling.

* CIMZIA vs placebo: p< 0.0001.
Response rates and p-values for PASI and PGA were estimated based on a logistic regression model where missing data were imputed using multiple imputation based on the MCMC method. Subject who escaped or withdrew (based on not achieving PASI 50 response) were treated as non-responders at Week 48.
Mean (SD) Dermatology Life Quality Index (DLQI) change from Baseline values are the unadjusted values. P-values for DLQI based on the model-adjusted estimates (not presented) using an ANCOVA model. Missing data were imputed using LOCF. Results are from the Randomized Set

The key results of the CIMPACT trial are presented in Table 22.

Table 22: Clinical response in CIMPACT study at Week 12 and Week 16

	Week 12			**Week 16**		
	Placebo N=57	CIMZIA[a)] 200 mg Q2W N=165	CIMZIA 400 mg Q2W N=167	Placebo N=57	CIMZIA 200 mg Q2W N=165	CIMZIA 400 mg Q2W N=167
PASI 75	5%	61.3%*	66.7%*	3.8%	68.2%*	74.7%*
PASI 90	0.2%	31.2%*	34.0%*	0.3%	39.8%*	49.1%*
PGA clear or almost clear [b)]	1.9%	39.8%**	50.3%*	3.4%	48.3%*	58.4%*

[a)] CIMZIA 200 mg administered every 2 weeks preceded by a loading dose of 400 mg at Week 0, 2, 4.
[b)] PGA 5 catergory scale. Treatment success of "clear" (0) or "almost clear"(1) consisted of no signs of psoriasis or normal to pink coloration of lesions, no thickening of the plaque, and none to minimal focal scaling.
* CIMZIA vs placebo: p< 0.0001. ** CIMZIA vs Placebo < 0.001. Response rates and p-values based on a logistic regression model. Missing data were imputed using multiple imputation based on the MCMC method.
Results are from the Randomized Set.

In the CIMPACT study, at Week 12, the Cimzia 400 mg every 2 weeks dosing schedule demonstrated superiority against Enbrel 50 mg twice weekly in PASI 75 response rate (66.7% and 53.3% respectively , p<0.05). The Cimzia 200 mg every 2 weeks dosing schedule demonstrated non-inferiority against Enbrel 50 mg twice weekly in PASI 75 response rate (61.3%, difference between Enbrel and Cimzia 200 mg every 2 weeks was 8.0%, 95% CI -2.9, 18.9) based on a pre-specified non-inferiority margin of 10%.

In all 3 studies, the PASI 75 and PGA clear or almost clear response rate were significantly greater for Cimzia compared to placebo starting at Week 4.

Both doses of Cimzia demonstrated efficacy compared to placebo regardless of age, gender, body weight, BMI, psoriasis disease duration, previous treatment with systemic therapies and previous treatment with biologics.

At Week 48, Cimzia treated patients with nail psoriasis reported improvements from baseline in nail psoriasis as measured by the Modified Nail Psoriasis Severity Index (mNAPSI). This was not tested for statistical significance.

Maintenance of response
In an integrated analysis of CIMPASI-1 and CIMPASI-2, among patients who were PASI 75 responders at Week 16 and received Cimzia 400 mg every 2 weeks (134 patients) or Cimzia 200mg every 2 weeks (132 patients), the maintenance of response rates at Week 48 was 98.0% and 87.5%, respectively. Among patients who were PGA clear or almost clear at Week 16 and received Cimzia 400 mg every 2 weeks (103 patients) or Cimzia 200 mg every 2 weeks (95 patients), the maintenance

of response rate at Week 48 was 85.9% and 84.3% respectively. After an additional 96 weeks of open-label treatment (Week 144) the maintenance of response was evaluated. Twenty-one percent of all randomised subjects were lost to follow-up before Week 144. For Cimzia 200 mg every 2 weeks treatment group, the maintenance of response at Week 144, with the continued open-label treatment of Cimzia 200 mg every 2 weeks, Cimzia 200 mg every 2 weeks was 84.5%, for PASI 75, and 78.4%, for PGA clear or almost clear. For the treatment group receiving Cimzia 400 mg every 2 weeks during 48 weeks, followed by Cimzia 200 mg every 2 weeks of open-label treatment, the maintenance of response at week 144 was 84.7% for PASI 75 and 73.1% for PGA clear or almost clear. These response rates were based on a logistic regression model where missing data were imputed over 48 or 144 weeks, using multiple imputation (MCMC method).

In the CIMPACT study, among PASI75 responders at Week 16 who received Cimzia 400 mg every 2 weeks and were re-randomized to either Cimzia 400 mg every 2 weeks (48 patients), Cimzia 200 mg every 2 weeks, or placebo, there was a higher percentage of PASI 75 responders at Week 48 in the Cimzia groups as compared to placebo (98.0%, 80.0%, and 36.0%, respectively). Among PASI75 responders at Week 16 who received Cimzia 200 mg every 2 weeks and were re-randomized to either Cimzia 400 mg every 4 weeks, Cimzia 200 mg every 2 weeks (36 patients), or placebo, there was also a higher percentage of PASI 75 responders at Week 48 in the Cimzia groups as compared to placebo (88.6%, 79.5%, and 45.5%, respectively). After an additional 96 weeks of open-label treatment (Week 144), the maintenance of PASI 75 response in patients re-randomized to Cimzia 400 mg every 2 weeks or Cimzia 200 mg every 2 week was 83.3% in both groups. Non-responder imputation was used for missing data.

Summary of stratification by bodyweight
PASI75 responder rates from CIMPASI-1, CIMPASI-2 and CIMPACT at Week 16, and from CIMPASI- 1 and CIMPASI-2 at Week 48, stratified by dose (Cimzia 200 mg every 2 weeks vs Cimzia 400 mg every 2 weeks) and body weight (<90kg vs ≥ 90kg) are shown in Table 23.

Table 23: PASI75 Responder Rates at Week 16 and Week 48 by Weight Category in Phase III Psoriasis Studies

	Body weight <90kg			**Body weight ≥90kg**		
Week 16 (CIMPASI-1, CIMPASI-2, CIMPACT) (NRI)						
	PBO N=84	**CZP 200mg Q2W N=175**	**CZP 400mg Q2W N=206**	**PBO N=73**	**CZP 200mg Q2W N=176**	**CZP 400mg Q2W N=136**
PASI75	8.0	81.0	81.9	5.6	63.5	72.3
Week 48 (CIMPASI-1, CIMPASI-2) (NRI)						
	CZP 200mg Q2W N=80		**CZP 400mg Q2W N=97**	**CZP 200mg Q2W N=106**		**CZP 400mg Q2W N=78**
PASI75	71.3		77.3	56.6		67.9

NRI = non-responder imputation

Quality of life / Patient reported outcomes
In CIMPASI-1 and CIMPASI-2 studies, Cimzia treated patients reported significant improvement from baseline compared to placebo in skin condition-related quality of life as measured by the DLQI from Week 2 through Week 16 and an increasingly larger proportion of patients treated with Cimzia achieved a DLQI 0 or 1 as compared with placebo. This proportion was maintained through Week 48. Cimzia treated patients reported significant improvement in the SF-36 mental component at Week 16 as compared to placebo. Improvements in DLQI outcomes were maintained through Week 144.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of Cimzia in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis patients are similar.

Absorption
Following subcutaneous administration, peak plasma concentrations of Cimzia were attained between 54 and 171 hours postinjection. Cimzia has a bioavailability (F) of approximately 80% (range 76% to 88%) following subcutaneous administration compared to intravenous administration. Cimzia has predictable dose related exposure with an approximately linear relationship between the dose administered and the maximum plasma concentration (C_{max}) or the area under the plasma concentration versus time curve (AUC). Pharmacokinetics observed in patients with rheumatoid arthritis were consistent with those seen in healthy subjects.

Distribution
The apparent volume of distribution (V/F) was estimated at 8.01 L in a population pharmacokinetic analysis of patients with rheumatoid arthritis and at 4.71 L in a population pharmacokinetic analysis of patients with plaque psoriasis.

Metabolism
PEGylation, the covalent attachment of PEG polymers to peptides, delays the elimination of these entities from the circulation by a variety of mechanisms, including decreased renal clearance, decreased proteolysis, and decreased immunogenicity. Accordingly, Cimzia is an antibody binding fragment (Fab') conjugated with PEG in order to extend the terminal plasma elimination half-life of the Fab' to a value comparable with a whole antibody product. The terminal elimination phase half-life ($t_{1/2}$) was approximately 14 days for all doses tested. Clearance following subcutaneous dosing was estimated to be 21.0 mL/h in a rheumatoid arthritis population pharmacokinetic analysis, with an intersubject variability of 30.8% (CV) and an interoccasion variability of 22.0%. When assessed using the previous ELISA method, the presence of antibodies to Cimzia results in approximately a threefold increase in clearance. Compared with a 70 kg person, predicted clearance is 29% lower and 38% higher, respectively, for rheumatoid arthritis patients with extreme bodyweights of 40 kg and 120 kg, but pharmacodynamic exposure-response analysis showed that no additional therapeutic benefit would be expected from a weight adjusted dose regimen. The metabolism of certolizumab pegol has not been studied in human subjects. The clearance following subcutaneous dosing in patients with plaque psoriasis was 14 ml/h with an inter-subject variability of 22.2% (CV). Population PK modelling revealed a trend toward higher apparent clearance resulting in lower plasma concentration and in some patients reduced efficacy, with increasing body weight and with development of antibodies to Cimzia.

Excretion
The route of elimination of Cimzia has not been studied in human subjects but studies in rats have shown that renal excretion is the major route of elimination of the deconjugated PEG component of Cimzia.

Renal impairment
Specific clinical studies have not been performed to assess the effect of renal impairment on the pharmacokinetics of Cimzia or its PEG fraction. However, population pharmacokinetic analysis based on subjects with mild renal impairment showed no effect of creatinine clearance. There are insufficient data to provide a dosing recommendation in moderate and severe renal impairment. The pharmacokinetics of the PEG (polyethylene glycol) fraction of Cimzia are expected to be dependent on renal function but have not been assessed in renal impairment.

Hepatic impairment
Specific clinical studies have not been performed to assess the effect of hepatic impairment on the pharmacokinetics of Cimzia.

Elderly
Specific clinical studies have not been performed in elderly subjects. However, no effect of age was observed in a population pharmacokinetic analysis in patients with rheumatoid arthritis in which 78 subjects (13.2% of the population) were aged 65 or greater and the oldest subject was aged 83 years. No effect of age was observed in a population pharmacokinetic analysis in adult patients with plaque psoriasis.

Paediatric
Cimzia has not been studied in children.

Gender
There was no effect of gender on the pharmacokinetics of Cimzia.

Pharmacokinetic/pharmacodynamic relationship
A population pharmacokinetic/pharmacodynamic analysis of phase II and phase III clinical study data from adult subjects with rheumatoid arthritis showed an exposure-response relationship between plasma concentration of Cimzia and efficacy using a maximum effect (E_{max}) model for ACR20 response. The typical average plasma concentration during the dose interval (C_{avg}) that produces half the maximum probability of ACR20 response (EC_{50}) was 17 µg/mL (95% CI: 10-23 µg/mL).

A population pharmacokinetic/pharmacodynamic analysis of Phase III clinical study data from adult subjects with plaque psoriasis showed an exposure-response relationship between certolizumab pegol plasma concentration and PASI with an EC90 of 11.1 µg/mL (95% CI: 0.8 – 21 ug/mL). The EC90 value was associated with a large variability. Heavier patients appeared to have lower Cimzia plasma concentrations than lower body weight patients (range: 42–198 kg), and heavier patients appeared to reach a steady-state clinical response later (e.g. 16 weeks for a 90 kg subject compared to 21 weeks for a 150 kg subject).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Cimzia was not genotoxic in the Ames test, the human peripheral blood lymphocytes chromosomal aberration assay, or the mouse bone marrow micronucleus assay.

Carcinogenicity
Long-term animal studies of Cimzia have not been conducted to assess its carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients are sodium chloride, sodium acetate and water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part the registration of this medicine.

6.3 SHELF LIFE

24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Storage at 2°C to 8°C. (Refrigerate. Do not freeze.)

Protect from light.

For patients: If needed, Cimzia may be stored at room temperature up to a maximum of 25°C for a single period of up to 10 days with protection from light. Once Cimzia has been stored at room temperature, it should not be placed back into the refrigerator and should be discarded if not used within the 10-day period.

6.5 NATURE AND CONTENTS OF CONTAINER

Cimzia injection is supplied in a carton containing two single use pre-filled glass syringes of 200 mg (1 mL) Cimzia and two alcohol pads or in a carton containing two*, six* or ten* single use pre-filled pens (AutoClicks®) of 200 mg (1 mL) Cimzia and two*, six* or ten* alcohol pads. The needle shield is styrene butadiene rubber which contains 7% epoxyprene, a derivative of natural rubber latex (see Section 4.4 Special Warnings and Precautions for Use).

*not currently distributed in Australia

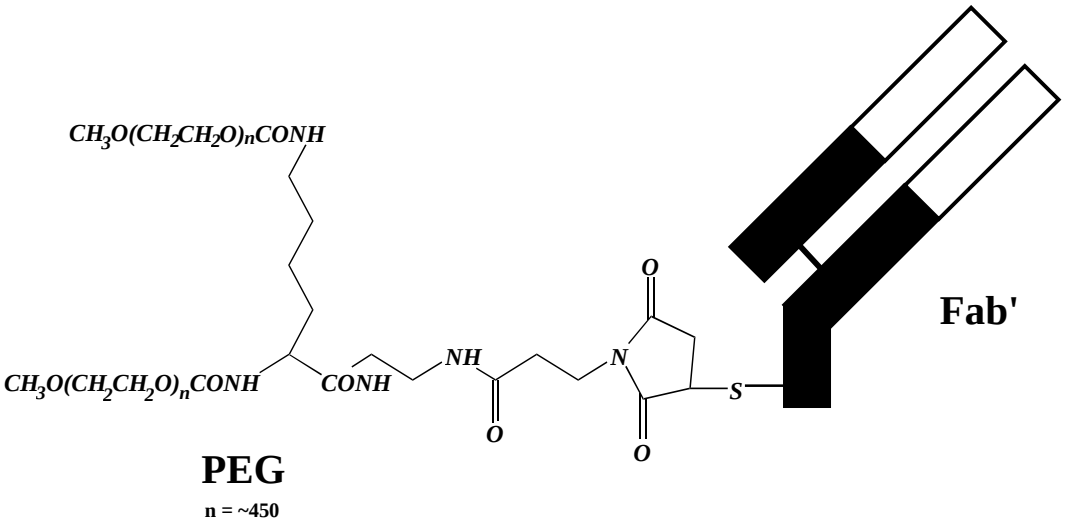
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Name: gHTNF40 Fab'40 kDa PEG
MW: approximately 90,000 Da

Chemical structure



CAS number
428863-50-7

The pH of the solution is approximately 4.7.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

20 January 2010

10 DATE OF REVISION

7 March 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.6	Update prospective pregnancy numbers.
4.8, 5.1	Addition of long-term clinical data for plaque psoriasis