19 September 2013
EMA/CHMP/458168/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cimzia

Procedure no. EMEA/H/C/001037/II/29

Marketing authorisation holder (MAH): UCB Pharma SA

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ANCOVA	analysis of covariance
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASAS20, 40, 50, 70	Assessment of SpondyloArthritis International Society 20%, 40%, 50%, 70% response criteria
ASAS5/6	Assessment of SpondyloArthritis International Society at least 20% improvement in 5 of 6 domains, including spinal mobility (i.e. lateral spinal flexion, BASMI) and CRP as a more objective measure
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
ASspiMRI	ankylosing spondylitis spine MRI scoring system for disease activity
axSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASADI50	Bath Ankylosing Spondylitis Disease Activity Index improvement of at least 50% compared with Baseline
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
CD	Crohn's disease
CI	confidence interval
CQA	Clinical Quality Assurance
CRF	case report form
CRP	C-reactive protein
CS	Completer Set
CSR	Clinical Study Report
CZP	certolizumab pegol
DMARD	disease-modifying antirheumatic drug
EU	European Union
Fab′	fragment antigen binding prime
FAS	Full Analysis Set
HLA-B27	human leukocyte antigen B27
HRQoL	health-related quality of life
LOCF	last observation carried forward
LS	least squares
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCID	minimal clinically important difference
MCS	Mental Component Summary
mNY	modified New York Criteria for ankylosing spondylitis
MRI	magnetic resonance imaging
MRIS	Magnetic Resonance Imaging Set
nr-axSpA	non-radiographic axial spondyloarthritis

NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
OC	observed case
OR	odds ratio
PCS	Physical Component Summary
PEG	polyethylene glycol
PF	Physical Function
PFS	prefilled syringe
PPS	Per Protocol Set
PtGADA	Patient's Global Assessment of Disease Activity
Q2W	every 2 weeks
Q4W	every 4 weeks
RA	rheumatoid arthritis
RS	Randomized Set
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SCE	Summary of Clinical Efficacy
SD	standard deviation
sDMARDs	synthetic disease modifying antirhematic drugs
SF-36	Short-Form 36-item Health Survey
SPARCC	Spondyloarthritis Research Consortium of Canada
STIR	short-tau-inversion recovery
TB	tuberculosis
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, UCB Pharma SA submitted to the European Medicines Agency on 17 December 2012 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Cimzia	Certolizumab pegol	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a)	Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of the indication for the treatment of adult patients with active axial spondyloarthritis (AxSpA), including patients with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis who have had an inadequate response to NSAIDs. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.8 and 5.1 of the SmPC. The package leaflet was proposed to be updated in accordance.

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0208/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0208/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: K Dunder

Co-Rapporteur: J Borvendég

Submission date:	17 December 2012
Start of procedure:	25 January 2013
Co-Rapporteur's preliminary assessment report circulated on:	25 February 2013
Joint Rapporteur's updated assessment report circulated on:	25 March 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2013
MAH's responses submitted to the CHMP on:	19 July 2013
Joint Rapporteur's assessment report on the MAH's responses circulated on:	21 August 2013
PRAC RMP advice and assessment overview adopted by PRAC	05 September 2013
CHMP opinion:	19 September 2013

2. Scientific discussion

2.1. Introduction

Cimzia (certolizumab pegol) is a humanized fragment antigen binding prime (Fab') conjugated to polyethylene glycol (PEG). Certolizumab pegol neutralizes human TNFα bioactivity and inhibits the production of inflammatory cytokine by monocytes. In EU/EEA, Cimzia is approved in combination with methotrexate (MTX), for the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients.The recommended starting dose of Cimzia for adult RA patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. After the starting dose, the recommended maintenance dose for RA adult patients is 200 mg every 2 weeks. MTX should be continued during treatment with Cimzia where appropriate.

The purpose of this application is to extend the indication of Cimzia for the treatment adult patients with active AxSpA, including patients with AS and non-radiographic AxSpA (nr-axSpA) who have had an inadequate response to NSAIDs.

AxSpA refers to spondyloarthropathy with predominantly axial involvement and comprises the disease sub-group of ankylosing spondylitis, as well as the disease sub-group with little or no changes on plain radiographs, referred to as nr-axSpA.

The Assessments in Spondyloarthritis International Society (ASAS) criteria for classification of axSpA, are:

- Back pain of ≥3 month duration at age of onset <45, and either of the three is true:

  1. The subject has active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA and in addition at least one of the below clinical features.

2. The subject has definitive sacroiliitis (grade ≥2 bilaterally or ≥3 unilaterally) on x-ray and in addition at least one of the below clinical features.
3. The subject is HLA B27 positive and has at least two further of the below clinical features.

The clinical features include:

- HLA B27 positivity
- inflammatory back pain
- arthritis
- enthesitis
- uveitis
- dactylitis
- psoriasis
- Crohn's/colitis
- elevated CRP
- good response to NSAIDs in the past
- family history for SpA

The modified NY criteria for AS (mNY) require x-ray findings of sacroiliitis grade ≥2 bilaterally or grade 3-4 unilaterally. In addition, at least 1 of the 3 following clinical criteria must be fulfilled:

- Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest.
- Limitation of motion of the lumbar spine in the sagittal and frontal planes.
- Limitation of chest expansion relative to normal values correlated for age and sex.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trial that support this submission, AS001, was performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of the clinical study

Study identifier	Obectives of the study	Study design and type of control	Test product / dosage regimen / route of administration	Number of randomized subjects	Duration of treatment	Study status / type of report
AS001	Efficacy and safety	Randomized, double-blind, parallel-group, placebo-controlled Placebo	Placebo or CZP 200mg/mL in prefilled syringe/ CZP 400mg at Weeks 0, 2, and 4 followed by CZP 200mg Q2W or CZP 400mg Q4W/sc	325 Subjects with active axSpA	24 weeks	Ongoing/interim

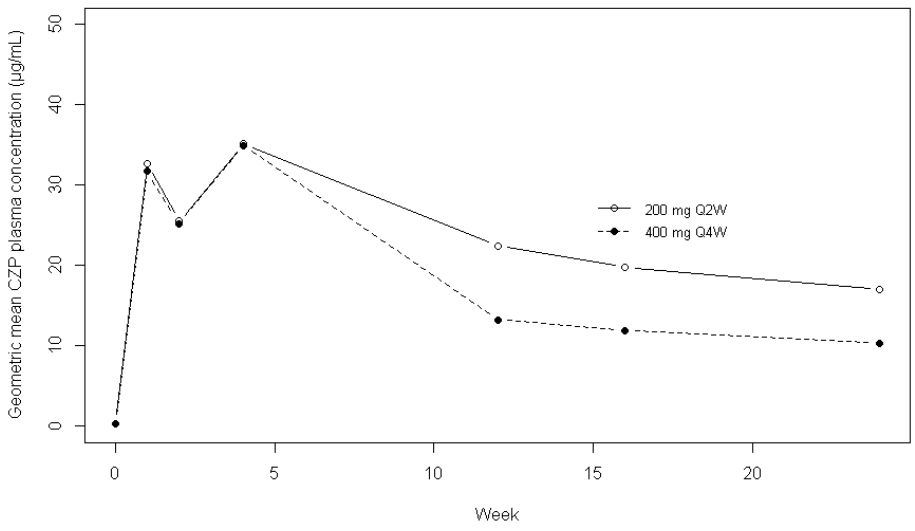
2.3.2. Pharmacokinetics

Pharmacokinetics in target population

The pharmacokinetics of CZP in AxSpA patients was investigated in study AS001 and the interim results following 24 weeks of treatment with either placebo, 200 mg Q2W or 400 mg Q4W were reported. Plasma samples for the measurement of CZP concentrations were taken at Baseline and Weeks 1, 2, 4, 12, 16, 24, Early Withdrawal, and safety follow-up (SFU). A plot of geometric mean CZP plasma concentration vs time is shown in Figure 1. The CZP 200mg Q2W and the CZP 400mg Q4W treatment groups are represented by open and solid symbols, respectively.

At Weeks 0, 2, and 4, subjects in both CZP groups were treated with loading doses of CZP 400mg; the mean (geometric) plasma CZP concentration at these time points were similar between treatment groups. After completion of the loading dose phase, the CZP trough concentrations at Weeks 12, 16, and 24 were lower than at the early weeks. At Weeks 12, 16, and 24, plasma CZP trough concentrations were approximately 40% lower in the CZP 400mg Q4W group compared with the CZP 200mg Q2W group. There was a slight trend towards declining CZP concentration with time in both treatment groups. The CZP concentration at Week 24 was approximately 20% lower compared to Week 12. The variability in observed trough concentration at Week 12, 16 and 24 was moderate to high, 45% to 72% (geometric %CV).

Figure 1 Geometric mean certolizumab plasma concentration (Per protocol, observed cases)



Immunologic measurements

Plasma samples for the measurement of anti-CZP antibodies were taken at Baseline and Weeks 1, 2, 4, 12, 16, 24, Early Withdrawal, and SFU.

The majority of subjects (96.7%) were negative for anti-CZP antibodies; only 10 subjects (3.3%) were positive for anti-CZP antibodies. For the subjects who were positive for anti-CZP antibodies, mean (geometric) plasma CZP concentrations were markedly lower at Weeks 12, 16, and 24 than those observed in subjects who were negative for anti-CZP antibodies. At Week 24, the geometric mean CZP plasma concentration in antibody positive patients was 4.23 µg/mL and 1.20 µg/mL for 200 mg Q2W and 400 mg Q4W dosing regimens, respectively.

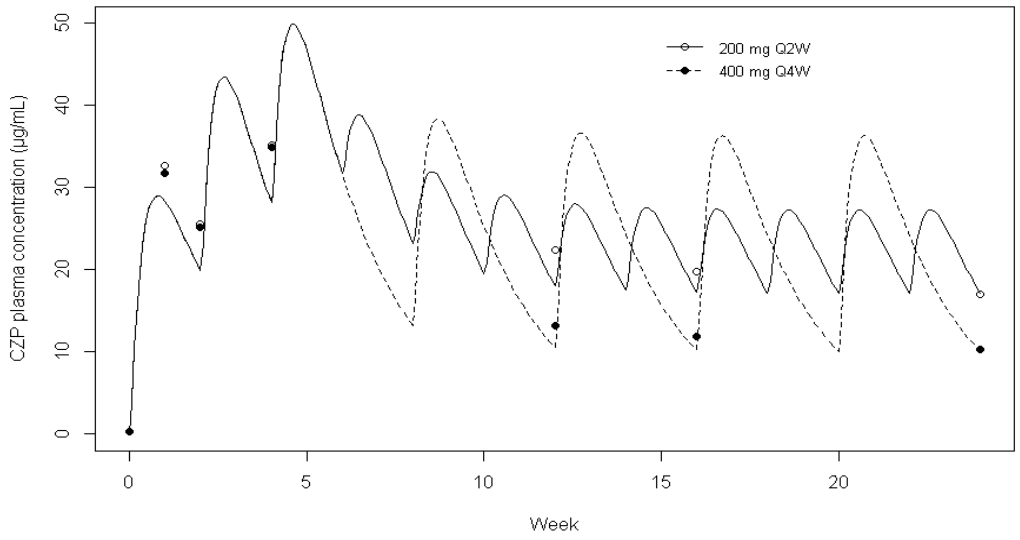
The number of patients with positive anti-CZP antibody status was low, however, plasma concentration in these patients were substantially lower compared to antibody negative patients. A subgroup analysis of ASAS20 response (Assessment of Axial SpondyloArthritis International Society 20% response criteria), was made, taking anti-CZP antibody status into account. Due to the low number of anti-CZP positive patients, the confidence interval of the proportion of responders was very wide and no meaningful conclusion can be drawn regarding efficacy in this subgroup.

2.3.3. Discussion on clinical pharmacology

CZP dosing regimens in AS001 were chosen on the basis that these doses have been efficacious for the treatment of RA in clinical studies and are the recommended dosing regimens in RA.

The observed geometric mean plasma concentration of CZP was compared to simulated values using the previously reported PK model for RA patients. Observed plasma concentration was in line with the model predictions (See Figure 2) confirming that the AxSpA patients did not exhibit substantially different PK profile compared to RA patients. The slight decrease seen when comparing Week 24 observations to Week 12 observations seems to be reasonably in line with the PK model.

Figure 2 Observed geometric mean CZP concentrations compared to simulated PK profile



The pharmacokinetics of CZP in AxSpA patients receiving 200 mg Q2W or 400 mg Q4W CZP was adequately characterized. The observed concentration was consistent with what has been seen in RA patients. The difference in plasma concentration between the two dosing regimen was in line with expectations.

The plasma concentration of CZP in patients with positive anti-CZP antibody status was markedly lower compared to patients without antibodies towards CZP. No conclusion can be drawn on whether positive anti-CZP antibody status would alter the efficacy of CZP due to the small number of subjects with a positive anti-CZP status.

2.3.4. Conclusions on clinical pharmacology

The pharmacokinetics of CZP in AxSpA patients receiving 200 mg Q2W or 400 mg Q4W CZP was adequately characterized. The observed concentration was consistent with what has been seen in RA patients. The difference in plasma concentration between the two dosing regimen was in line with expectations. The recommended starting dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. After the starting dose, the recommended maintenance dose of Cimzia for adults patients with axial spondyloarthritis is 200 mg every 2 weeks or 400 mg every 4 weeks. The plasma concentration of CZP in patients with positive anti-CZP antibody status was markedly lower compared to patients without antibodies towards CZP. No conclusion can be drawn on whether positive anti-CZP antibody status would alter the efficacy of CZP due to the small number of subjects with a positive anti-CZP status.

2.4. Clinical efficacy

2.4.1. Main study

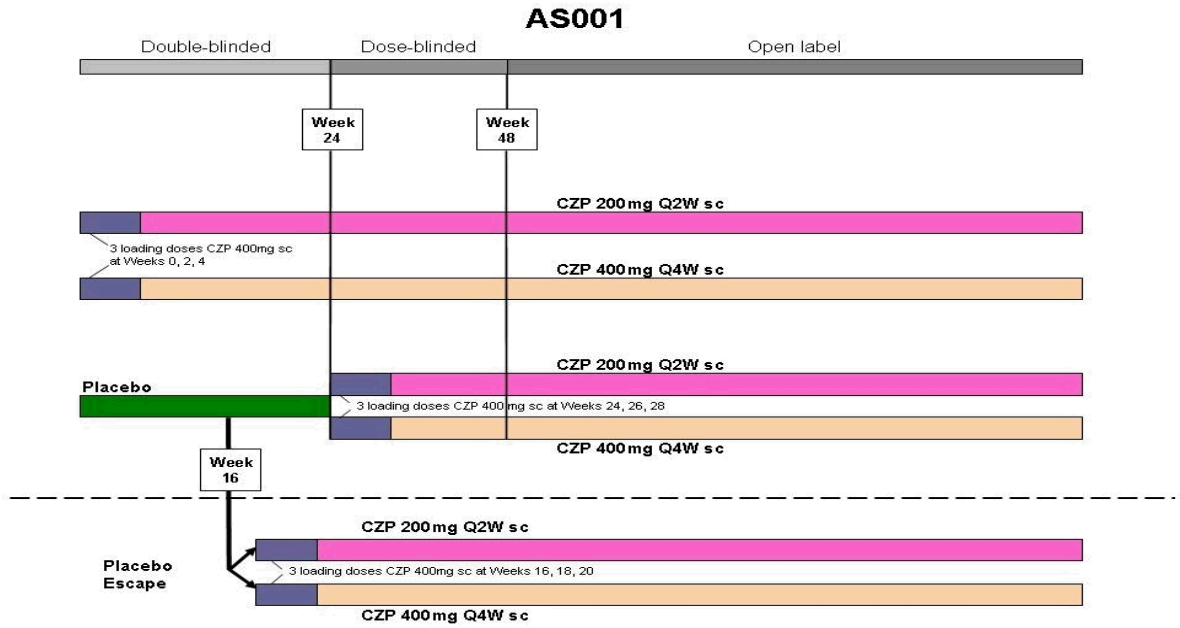
The title of the main study is: Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of certolizumab pegol in subjects with axial spondyloarthritis.

Methods

AS001 is a multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study designed to evaluate the safety and efficacy of CZP in subjects with adult onset active axSpA (including AS). The study was designed to enroll an equal number of AS and nr-axSpA patients, thus ensuring representation of the entire AxSpA population while allowing comparison between axSpA subgroups.

The AS001 study includes 5 study periods: Screening, the Double-Blind Treatment Period (up to Week 24), the Dose-Blind Treatment Period (Week 24 to Week 48), the Open-Label Period (Week 48 to Week 204), and the Safety Follow-Up Period (Week 204 to Week 212). The Screening Period and the Double-Blind Treatment Period (up to Week 24; DB1) are complete and, together with additional clinical safety data after the DB1 lock to 31 May 2012, form the basis of this submission. Sacroiliac joint and spinal MRIs were performed on subjects in the MRIS substudy (n=153) and scored by both the SPARCC (sacroiliac joint) and ASspiMRI (spine) scoring methods.

Figure 3 AS001 study design



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

Study participants

Main inclusion criteria:

- Adult onset axSpA of at least 3 months symptom duration as defined by specified ASAS criteria. Half of subjects who met the ASAS criteria should NOT have fulfilled the mNY criteria for definite diagnosis of AS.
- Active disease as defined by:
    - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4,
    - Spinal pain ≥4 on a 0 to 10 Numerical Rating Scale (NRS) (from BASDAI item 2), and
    - Objective signs of inflammation: C-reactive protein (CRP) > upper limit of normal and/or current evidence (i.e., within the last 3 months from Screening) for sacroiliitis on MRI as defined by ASAS classification criteria.
- Intolerance or inadequate response to at least 1 NSAID, defined as lack of response to at least 30 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID or lack of response to treatment with at least 2 NSAIDs at the maximum tolerated dose for 2 weeks each.

Main exclusion criteria:

- Exposure to more than 1 anti-TNFα agent prior to the Baseline Visit.
- Primary failure to any anti TNFα therapy (defined as no response within the first 12 weeks of treatment with the anti-TNFα), or
- Exposure to more than 2 previous biological agents for AxSpA.

Treatments

During the 24-week Double-Blind Treatment Period, subjects were treated with either CZP 200mg Q2W, CZP 400mg Q4W, or placebo.

The dosing regimens for other commercially available subcutaneous (sc) anti-TNFα agents for the treatment of AS are based on the dosing regimens for RA and show similar efficacy and safety profiles in both indications. Therefore, the selected CZP dosing regimens in AS001 were chosen on the basis that these doses have been efficacious for the treatment of RA in clinical studies, are the recommended dosing regimens in RA, and would be expected to have similar efficacy in axSpA.

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

Injections were given sc in the lateral abdominal wall or upper outer thigh. During each dosing visit, if 2 injections were being administered (i.e., CZP 400mg as 2 injections of 200mg each, CZP 200mg as 1 injection of CZP and 1 injection of placebo, or placebo as 2 injections of saline) each of the 2 injections were to be administered at a separate injection site.

Subjects receiving placebo who did not achieve at least a minimal response (defined as those subjects who did not achieve Axial Spondyloarthritis International Society 20% response criteria [ASAS20]) at both Weeks 14 and 16 were allocated to escape treatment (randomized in a 1:1 ratio to receive CZP 200mg Q2W or CZP 400mg Q4W) from Week 16 onwards.

Permitted concomitant treatments (medications and therapies)

The following axSpA medications/treatments were allowed during this study from Baseline onward, with the specified restrictions:

- NSAIDs/cyclooxygenase-2 inhibitors: doses were to be stable in the 2 weeks prior to an arthritis assessment.
- Analgesics (e.g., acetaminophen or paracetamol, narcotics) were permitted except ad hoc as needed (prn) usage within the 24-hour period prior to any assessments.
- Corticosteroids (see Section 3.5.5.3 for prohibited corticosteroids):
    - Oral (maximum allowed ≤10mg daily total prednisone equivalent Subjects were permitted to change their oral corticosteroid therapy dose equivalent and regimen only after Week 48
    - Intra-articular (ia) Only after the first 48 weeks of the study, 1 ia injection of up to 50mg prednisone equivalent could have been given at most every 4 months.
    - Intravenous (iv) Only after the first 48 weeks of the study, hydrocortisone administered iv only for the purposes of stress dosing for a surgical procedure under general or spinal anesthesia was permitted.
- Specific sDMARDs only (SSZ and/or HCQ and/or MTX: maximum SSZ ≤3g daily; HCQ ≤400mg daily; MTX ≤25mg weekly allowed. No change in dose or dose regimen was allowed during the first 48 weeks of the study except for reasons of intolerance, where the sDMARD dose could be decreased but not discontinued. Changes in dosages were permitted after the first 48 weeks of the study. No change was permitted in the route of administration for MTX (intramuscular [im], sc, or oral) in the first 48 weeks of the study.

Objectives

The primary objective of the study was to demonstrate the efficacy of CZP administered subcutaneously at the doses of CZP 200mg every 2 weeks (Q2W) and CZP 400mg every 4 weeks (Q4W) after a loading dose of CZP 400mg at Weeks 0, 2, and 4 on the signs and symptoms of active axSpA.

The secondary objectives of the study were to assess the effects on safety and tolerability and to demonstrate the effects of CZP on:

- Health outcomes
- Partial remission
- Spinal mobility
- Structural damage and inflammation in the subpopulation of subjects with MRI

The other objectives of the study were to assess the effect of CZP treatment on:

- Enthesitis
- Direct medical resource utilization
- Subject's health status
- Structural damage in the subpopulation of subjects with x-rays
- Assessment of subject symptomatic state

Outcomes/endpoints

The primary efficacy variable was ASAS20 response at Week 12.

The ASAS20 response is defined as an improvement of at least 20% and absolute improvement of at least 1 unit on a 0 to 10 NRS in at least 3 of the 4 following domains:

- Patient's Global Assessment of Disease Activity
- Pain assessment (the total spinal pain NRS score)
- Function (represented by BASFI)
- Inflammation (the mean of the BASDAI Questions [Q] 5 and 6) concerning morning stiffness intensity and duration)

and absence of deterioration in the potential remaining domain (deterioration is defined as a relative worsening of at least 20% and an absolute worsening of at least 1 unit).

The key secondary efficacy variables of AS001 were:

- ASAS20 response at Week 24
- Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) to Weeks 12 and 24
- Change from Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) to Weeks 12 and 24
- Change from Baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) linear to Weeks 12 and 24

- Change from Baseline in sacroiliac Spondyloarthritis Research Consortium of Canada (SPARCC) scores (magnetic resonance imaging [MRI] parameter) to Week 12
- Change from Baseline in the ankylosing spondylitis spine MRI scoring system for disease activity (ASspiMRI-a) in the Berlin modification (MRI parameter) to Week 12

The BASFI is a validated disease-specific instrument for assessing physical function. It comprises 10 items relating to the past week. The NRS version was used for the answering options of each item on a scale of 0 ("Easy") to 10 ("Impossible"). The BASFI is the mean of the 10 scores, with lower scores indicating better physical function.

The BASMI linear characterizes the spinal mobility of subjects with AS. The BASMI linear is a disease-specific measure consisting of 5 clinical measures to reflect subject axial status: cervical rotation; tragus to wall distance; lumbar flexion (modified Schober test); intermalleolar distance, and lateral lumbar flexion. Each of the 5 movements is scored, and the mean of the 5 scores provides the BASMI score. The higher the BASMI score the more severe the patient's limitation of movement.

The BASDAI is a validated self-reported instrument which consists of six 10-unit horizontal NRSs to measure severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration, respectively) over the last week. The final BASDAI score ranges from 0 to 10, with lower scores indicating lower disease activity

The other secondary efficacy variables of AS001 were:

- ASAS20 response at Weeks 1, 2, 4, 8, 14, 16, 18, and 20
- ASAS 40/50/70 response and ASAS5/6 response at Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20, and 24
- Change from Baseline in all individual ASAS response criteria components to Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20, and 24
- Change from Baseline in nocturnal spinal pain NRS to Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20, and 24
- ASAS partial remission responder at Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20, and 24
- Change from Baseline in the Short-Form 36-item Health Survey (SF-36) Physical Component Summary (PCS) and Physical Function (PF) domain to Weeks 4, 8, 12, 16, 20, and 24.
- Change from Baseline in BASDAI to Weeks 1, 2, 4, 8, 14, 16, 18, and 20
- BASDAI50 (at least 50% improvement from Baseline in BASDAI) responders at Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20, and 24
- Change from Baseline in Fatigue (NRS; from BASDAI) to Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20, and 24.
- Change from Baseline to Weeks 1, 2, 4, 8, 12, 16, 20, and 24 in:
  - BASMI linear (not at Weeks 12 and 24)
  - Lumbar flexion (modified Schober test)
  - Tragus-to-wall distance
  - Occiput-to-wall distance
  - Chest expansion
  - Cervical rotation angle
  - Maximal intermalleolar distance

- Lateral lumbar flexion

- Change from Baseline in daily pain scores to Week 4
- Change from Baseline in CRP to Weeks 1, 2, 4, 8, 12, 16, 18, 20, and 24
- Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) to Weeks 1, 2, 4, 8, 12, 16, 18, 20, and 24
- Work Productivity Survey (WPS) responses at Weeks 4, 8, 12, 16, 20, and 24
  - Employment status
  - Number of work days missed due to arthritis
  - Number of days with productivity at work reduced by half or more due to arthritis
  - Interference of arthritis on work productivity (work outside of home)
  - Number of days with no household work due to arthritis
  - Number of days with productivity in household work reduced by half or more due toarthritis
  - Number of family, social, or leisure activities days missed due to arthritis
  - Number of days with outside help hired due to arthritis
  - Interference of arthritis on household work productivity

The ASAS criteria for 40%, 50%, or 70% improvement are defined as relative improvements of at least 40%, 50%, or 70% and absolute improvement of at least 2 units on a 0 to 10 NRS in at least 3 of the 4 domains and no worsening at all in the remaining domain.

Other efficacy variables of AS001 presented were

- Change from Baseline in enthesitis (Maastricht Ankylosing Spondylitis Enthesitis Score; MASES) at Weeks 1, 2, 4, 8, 12, 16, 18, 20, and 24
- Change from Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) at Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20, and 24
- Minimal clinically important difference (MCID) response at Weeks 1, 2, 4, 8, 12, 14, 16, 18, 20, and 24 for Total and nocturnal spinal pain, BASFI, BASDAI and SF-36 PCS.

Sample size

Based on published data with other anti-TNFα for the mNY definitive criteria subgroup (Inman et al, 2008), the anticipated difference from placebo for the active treatment groups in ASAS20 was greater than 38%. Since the modified NY Criteria subgroup included subjects with prior anti-TNFα exposure, the difference was assumed to be somewhat smaller (33%). Although the effect was not expected to be diminished for the entire axSpA population, a more conservative assumption of 30% for the difference was made. Therefore, a sample size of 105 subjects for each treatment group was sufficient to detect statistically significant differences in ASAS20between an active and placebo group with at least 99% power.

By ensuring that half of the subjects were in the AS subgroup, the determined sample size was also sufficient to detect a statistically significant difference between the active treatment groups and placebo with 90% power, assuming a difference of 33%.

Randomisation

Subjects were allocated to treatment in a 1:1:1 ratio (CZP 200mg Q2W: CZP 400mg Q4W: placebo). An interactive voice response system (IVRS) was used for subject registration as well as randomization and treatment administration.

Randomization was stratified on:

- Site
- Fulfilment of modified NY criteria (Yes/No)
- Prior anti-TNFα exposure (Yes/No)

Blinding (masking)

Due to differences in presentation and viscosity between active and placebo, special precautions were taken in order to ensure blinding of the study. Pharmacokinetic, antibody, and CRP data were to be provided only once the study was unblinded. From Week 24 onward, all subjects were treated with CZP (including the subjects originally randomized to placebo). The Investigators and subjects remained blinded to their allocated CZP dose regimen until the subject reaches his/her Week 48 Visit. Study treatments were administered by dedicated unblinded trained site personnel.

Statistical methods

The study was powered for the primary variable, and other variables from the hierarchical test procedure were not utilized. Five analysis sets were defined for purposes of the efficacy analyses:

1. The Randomized Set (RS) consisted of all subjects randomized into the study with an intention to treat.
2. The Full Analysis Set (FAS) consisted of all subjects in the RS who received at least 1 dose of study medication, had a valid Baseline, and had a valid post-Baseline efficacy measurement for the ASAS20. The ASAS response criteria measurement had to be obtained through to Week 12, ie, at least 1 post-Baseline ASAS response criteria measurement had to be available.
3. The Per Protocol Set (PPS) consisted of subjects in the FAS who had completed a minimal exposure of 12 weeks in the treatment regimen without any major protocol deviations that could have influenced the validity of the data for the primary efficacy variables. Post-Baseline deviations did not necessarily lead to exclusion of a subject from PPS analyses but could have led to exclusion of ASAS20 data.
4. The Completer Set (CS) consisted of subjects in the FAS who had completed 24 weeks of the randomized treatment regimen with valid 24 week measurements.
5. The Magnetic Resonance Imaging Set (MRIS) consisted of all subjects participating in the MRI substudy. Only subjects that had valid MRI assessments at Baseline and at Week 12 were considered.

The primary analyses of the primary variable were performed for the RS by imputation of missing values. For sensitivity analyses, the FAS (with imputation), PPS (with imputation), and the CS (with imputation) were utilized. For efficacy displays over time, in addition to the RS with imputation, a RS without imputation (RS [OC]) was utilized. Analyses concerning the MRI and x-ray parameters were performed using the MRIS.

The analyses on the primary variable were repeated for the AS subpopulation as well as for the nr-axSpA subpopulation. Analyses on all secondary variables were repeated for the AS subpopulation.

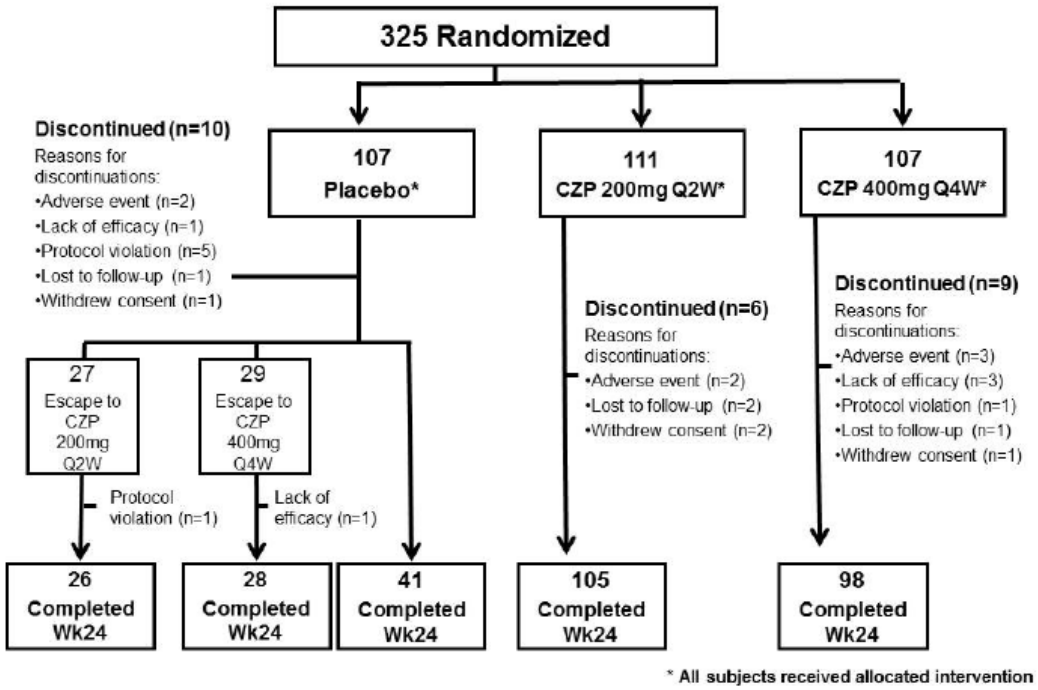
For the AS subpopulation, the ASAS20 analysis at Week 12 was not adjusted further, since statistical testing for European Union (EU) purposes was performed only if the hypothesis in the respective treatment group for the axSpA subjects could be rejected. The nr-axSpA subpopulation stratification subgroup was analyzed similarly.

In the statistical analysis of covariance (ANCOVA) models, Baseline was included as a covariate. By this the effect estimators were adjusted for potential Baseline imbalances, if Baseline had an impact on the variable to be analyzed (ie, change from Baseline). Region, mNY criteria, and prior anti-TNFα use were included as factors and their impact on the results analyzed.

Results

Participant flow

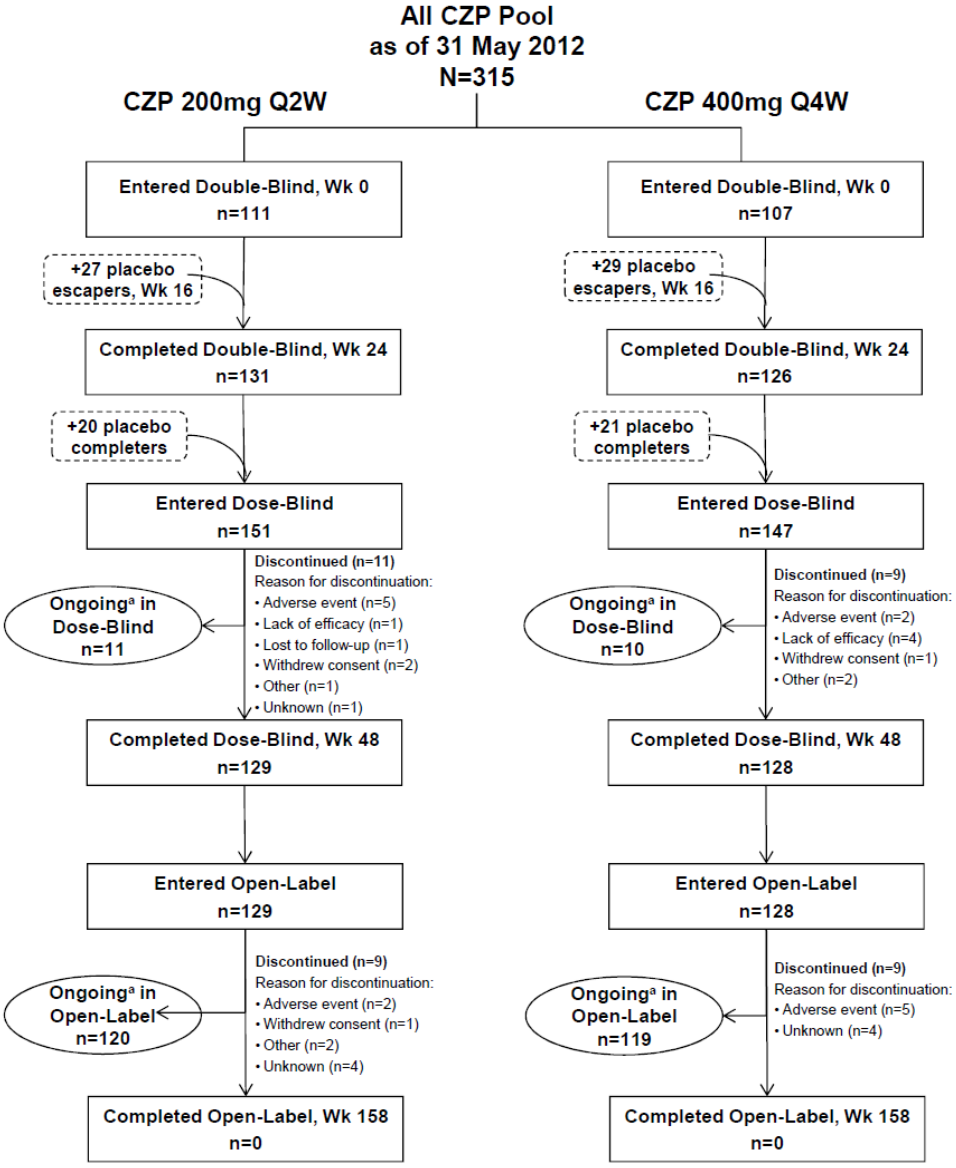
Figure 4 Disposition of subjects in the overall axSpA population (RS)



axSpA=axial spondyloarthritis; CZP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set
Note: Two subjects were randomized in error, were not treated, and were censored from the RS.

A total of 325 subjects with axSpA according to the ASAS classification criteria were randomized in AS001. At Week 0, a total of 218 subjects were randomized to CZP, and 107 subjects were randomized to placebo (Figure 4).

Figure 5 Flowchart of subject disposition AS001 up to the 31 May 2012 clinical cut



CZP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks; Wk=Week

Note: Placebo escapers are those subjects in the placebo group who escaped to CZP at Week 16. The CZP 200mg Q2W and CZP 400mg Q4W groups include subjects escaping from PBO to CZP at Week 16 and subjects switching from PBO to CZP at Week 24, utilizing their CZP data only.

Note: Three of the 5 subjects in the CZP 200mg Q2W group and 2 of the 4 subjects in the CZP 400mg Q4W group with a reason for discontinuation of "unknown" had AEs that resulted in permanent withdrawal of study medication.

[a] Indicates subjects ongoing in the study at the time of the data cutoff (31 May 2012).

At Week 16, a total of 56 placebo-escape subjects were re-randomized to CZP 200mg Q2W (27 subjects) or CZP 400mg Q4W (29 subjects) through to the end of the study. Most (91.7%) subjects completed the Double-Blind Treatment Period (up to Week 24). Overall, the most common reasons for discontinuation were adverse event and protocol violation (both, 2.2%).

Recruitment

AS001 a multicenter study involving 128 sites located in 16 countries in North America, Latin America, Western Europe, and Central/Eastern Europe. Of the randomized patients 27.1% were from North America, 10.2% from Latin America, 19.4% from West Europe and 43.4% from Eastern Europe.

Whereas the largest percentage of subjects in the AS subpopulation were from the Eastern Europe geographical region 55.1%, subjects in the nr-axSpA population were more evenly distributed among North America (27.2%), West Europe (34.7%), and Eastern Europe (29.3%). This is due to the fact that the Eastern Europe countries started enrolling first in Europe, and nr-axSpA subjects were difficult to enroll. Therefore, the enrollment arm of AS subjects was filled more quickly in the fastest enrolling region (Eastern Europe).

Conduct of the study

The original final AS001 Protocol (dated 25 Sep 2009) has undergone 4 global protocol amendments and 14 local protocol amendments to the date of submission of this procedure. The MAH became aware of a programming error in the IVRS which could have led to unblinding if not corrected. The MAH reported this incident to the regulatory authorities and committed to investigating the impact in further detail. Information derived from the conduct of the site audits suggested that although the potential for unblinding may have existed, there was no evidence available which supported that study data was changed or Investigator opinion biased in any way to change the outcome of the study variables. The affected subjects to be excluded from a sensitivity analysis were provided by the MAH after unblinding of the interim data. Notably, the potential unblinding could have occurred only from Week 16 on, after the primary efficacy endpoint data at Week 12 were already collected.

As part of the study entry criteria, subjects were required to fulfill the ASAS classification criteria for axSpA. A total of 7 subjects did not fulfill the ASAS classification criteria and were therefore protocol violations.

Baseline data

Table 1: Demographics summary and Baseline disease characteristics (RS, unless otherwise indicated)

	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W+ CZP 400mg Q4W	Overall
DEMOGRAPHICS					
Overall axSpA population	**N=107**	**N=111**	**N=107**	**N=218**	**N=325**
Age in years, median	38.0	36.0	40.0	38.0	38.0
Female, n (%)	42 (39.3)	44 (39.6)	39 (36.4)	83 (38.1)	125 (38.5)
AS subpopulation	**N=57**	**N=65**	**N=56**	**N=121**	**N=178**
Age in years, median	41.0	39.0	41.5	40.0	41.0
Female, n (%)	16 (28.1)	18 (27.7)	15 (26.8)	33 (27.3)	49 (27.5)
nr-axSpA subpopulation	**N=50**	**N=46**	**N=51**	**N=97**	**N=147**
Age in years, median	37.0	33.0	37.0	35.0	35.0
Female, n (%)	26 (52.0)	26 (56.5)	24 (47.1)	50 (51.5)	76 (51.7)
DISEASE CHARACTERISTICS					
Overall axSpA population	**N=107**	**N=111**	**N=107**	**N=218**	**N=325**
Met ASAS criteria, n (%)	104 (97.2)	109 (98.2)	105 (98.1)	214 (98.2)	318 (97.8)
HLA-B27 positive, n (%)	87 (81.3)	87 (78.4)	81 (75.7)	168 (77.1)	255 (78.5)
Symptom duration in years, median	7.68	6.92	7.93	7.75	7.73
Time since axSpA diagnosis in years, median	4.85	2.95	3.65	3.43	3.94
CRP in mg/L, median	15.0	12.7	12.3	12.5	13.9
CRP category, n (%)					
≤15mg/L	54 (50.5)	69 (62.2)	69 (64.5)	138 (63.3)	192 (59.1)
>15mg/L	53 (49.5)	42 (37.8)	38 (35.5)	80 (36.7)	133 (40.9)
Baseline BASDAI scores, Full Analysis Set (FAS[a]), mean (SD)	6.42 (1.67) N=106	6.49 (1.57) N=111	6.39 (1.46) N=107	6.44 (1.52) N=218	6.44 (1.56) N=324
Baseline BASMI linear scores, FAS[a], mean (SD)	3.99 (1.78) N=106	3.71 (1.58) N=111	3.81 (1.74) N=107	3.76 (1.66) N=218	3.84 (1.70) N=324
Baseline BASFI scores, FAS[a], mean (SD)	5.49 (2.13) N=106	5.26 (2.28) N=111	5.40 (2.34) N=107	5.33 (2.30) N=218	5.38 (2.25) N=324

Consistent with the study entry criteria, all (100%) subjects in the AS subpopulation had evidence of definitive sacroiliitis determined by x-ray; all other ASAS criteria were similar to the overall axSpA population (AS001 Week 24 CSR Table 2.4.2). A total of 54.4% of subjects in the nr-axSpA subpopulation had sacroiliitis detected via MRI. With the exception of sacroiliitis on imaging, fulfillment of ASAS criteria was similar between subjects with AS and nr-axSpA compared with the overall axSpA population.

Table 2 ASAS criteria – overall axSpA population (RS)

	PBO N=107	CZP 200mg Q2W N=111	CZP 400mg Q4W N=107	CZP 200mg Q2W+ CZP 400mg Q4W N=218	Overall N=325
ASAS classification fulfilled, n (%)					
Yes	104 (97.2)	109 (98.2)	105 (98.1)	214 (98.2)	318 (97.8)
No	3 (2.8)	2 (1.8)	2 (1.9)	4 (1.8)	7 (2.2)
Back pain ≥3 months and onset age <45 years, n (%)					
Yes	106 (99.1)	109 (98.2)	106 (99.1)	215 (98.6)	321 (98.8)
No	0	2 (1.8)	0	2 (0.9)	2 (0.6)
Unknown	1 (0.9)	0	1 (0.9)	1 (0.5)	2 (0.6)
Sacroiliitis on imaging[a], n (%)					
Yes	84 (78.5)	90 (81.1)	84 (78.5)	174 (79.8)	258 (79.4)
by MRI					
Yes	31 (29.0)	32 (28.8)	35 (32.7)	67 (30.7)	98 (30.2)
No	53 (49.5)	58 (52.3)	49 (45.8)	107 (49.1)	160 (49.2)
by x-ray					
Yes	57 (53.3)	65 (58.6)	56 (52.3)	121 (55.5)	178 (54.8)
No	27 (25.2)	25 (22.5)	28 (26.2)	53 (24.3)	80 (24.6)
No	17 (15.9)	17 (15.3)	21 (19.6)	38 (17.4)	55 (16.9)
Unknown	6 (5.6)	4 (3.6)	2 (1.9)	6 (2.8)	12 (3.7)
HLA-B27[a], n (%)					
Current and/or historical	76 (71.0)	81 (73.0)	75 (70.1)	156 (71.6)	232 (71.4)
Current					
Yes	75 (70.1)	76 (68.5)	72 (67.3)	148 (67.9)	223 (68.6)
No	18 (16.8)	14 (12.6)	20 (18.7)	34 (15.6)	52 (16.0)
Unknown	14 (13.1)	21 (18.9)	15 (14.0)	36 (16.5)	50 (15.4)
Historical					
Yes	67 (62.6)	78 (70.3)	69 (64.5)	147 (67.4)	214 (65.8)
No	20 (18.7)	13 (11.7)	20 (18.7)	33 (15.1)	53 (16.3)
Unknown	20 (18.7)	20 (18.0)	18 (16.8)	38 (17.4)	58 (17.8)

	PBO N=107	CZP 200mg Q2W N=111	CZP 400mg Q4W N=107	CZP 200mg Q2W+ CZP 400mg Q4W N=218	Overall N=325
Inflammatory back pain[a], n (%)					
Current and/or historical	105 (98.1)	109 (98.2)	106 (99.1)	215 (98.6)	320 (98.5)
Current					
Yes	104 (97.2)	109 (98.2)	105 (98.1)	214 (98.2)	318 (97.8)
No	3 (2.8)	2 (1.8)	2 (1.9)	4 (1.8)	7 (2.2)
Unknown	0	0	0	0	0
Historical					
Yes	101 (94.4)	108 (97.3)	103 (96.3)	211 (96.8)	312 (96.0)
No	5 (4.7)	3 (2.7)	3 (2.8)	6 (2.8)	11 (3.4)
Unknown	1 (0.9)	0	1 (0.9)	1 (0.5)	2 (0.6)
Arthritis[a], n (%)					
Current and/or historical	61 (57.0)	62 (55.9)	53 (49.5)	115 (52.8)	176 (54.2)
Current					
Yes	46 (43.0)	49 (44.1)	40 (37.4)	89 (40.8)	135 (41.5)
No	61 (57.0)	62 (55.9)	66 (61.7)	128 (58.7)	189 (58.2)
Unknown	0	0	1 (0.9)	1 (0.5)	1 (0.3)
Historical					
Yes	56 (52.3)	59 (53.2)	48 (44.9)	107 (49.1)	163 (50.2)
No	49 (45.8)	51 (45.9)	57 (53.3)	108 (49.5)	157 (48.3)
Unknown	2 (1.9)	1 (0.9)	2 (1.9)	3 (1.4)	5 (1.5)
Enthesitis (heel)[a], n (%)					
Current and/or historical	45 (42.1)	35 (31.5)	37 (34.6)	72 (33.0)	117 (36.0)
Current					
Yes	30 (28.0)	19 (17.1)	30 (28.0)	49 (22.5)	79 (24.3)
No	77 (72.0)	87 (78.4)	76 (71.0)	163 (74.8)	240 (73.8)
Unknown	0	4 (3.6)	1 (0.9)	5 (2.3)	5 (1.5)
Historical					
Yes	42 (39.3)	33 (29.7)	31 (29.0)	64 (29.4)	106 (32.6)
No	65 (60.7)	70 (63.1)	74 (69.2)	144 (66.1)	209 (64.3)
Unknown	0	7 (6.3)	2 (1.9)	9 (4.1)	9 (2.8)

	PBO N=107	CZP 200mg Q2W N=111	CZP 400mg Q4W N=107	CZP 200mg Q2W+ CZP 400mg Q4W N=218	Overall N=325
Uveitis[a], n (%)					
Current and/or historical	31 (29.0)	23 (20.7)	15 (14.0)	38 (17.4)	69 (21.2)
Current					
Yes	9 (8.4)	3 (2.7)	4 (3.7)	7 (3.2)	16 (4.9)
No	98 (91.6)	108 (97.3)	102 (95.3)	210 (96.3)	308 (94.8)
Unknown	0	0	1 (0.9)	1 (0.5)	1 (0.3)
Historical					
Yes	30 (28.8)	23 (20.7)	15 (14.0)	38 (17.4)	68 (20.9)
No	77 (72.0)	87 (78.4)	90 (84.1)	177 (81.2)	254 (78.2)
Unknown	0	1 (0.9)	2 (1.9)	3 (1.4)	3 (0.9)
Dactylitis[a], n (%)					
Current and/or historical	15 (14.0)	7 (6.3)	11 (10.3)	18 (8.3)	33 (10.2)
Current					
Yes	6 (5.6)	4 (3.6)	6 (5.6)	10 (4.6)	16 (4.9)
No	101 (94.4)	107 (96.4)	101 (94.4)	208 (95.4)	309 (95.1)
Unknown	0	0	0	0	0
Historical					
Yes	15 (14.0)	6 (5.4)	9 (8.4)	15 (6.9)	30 (9.2)
No	91 (85.0)	103 (92.8)	97 (90.7)	200 (91.7)	291 (89.5)
Unknown	1 (0.9)	2 (1.8)	1 (0.9)	3 (1.4)	4 (1.2)
Psoriasis[a], n (%)					
Current and/or historical	7 (6.5)	6 (5.4)	7 (6.5)	13 (6.0)	20 (6.2)
Current					
Yes	5 (4.7)	6 (5.4)	5 (4.7)	11 (5.0)	16 (4.9)
No	101 (94.4)	103 (92.8)	102 (95.3)	205 (94.0)	306 (94.2)
Unknown	1 (0.9)	2 (1.8)	0	2 (0.9)	3 (0.9)
Historical					
Yes	5 (4.7)	5 (4.5)	7 (6.5)	12 (5.5)	17 (5.2)
No	100 (93.5)	103 (92.8)	99 (92.5)	202 (92.7)	302 (92.9)
Unknown	2 (1.9)	3 (2.7)	1 (0.9)	4 (1.8)	6 (1.8)

	PBO N=107	CZP 200mg Q2W N=111	CZP 400mg Q4W N=107	CZP 200mg Q2W+ CZP 400mg Q4W N=218	Overall N=325
Crohn's disease/ulcerative colitis[a], n (%)					
Current and/or historical	8 (7.5)	5 (4.5)	5 (4.7)	10 (4.6)	18 (5.5)
Current					
Yes	7 (6.5)	5 (4.5)	4 (3.7)	9 (4.1)	16 (4.9)
No	100 (93.5)	104 (93.7)	103 (96.3)	207 (95.0)	307 (94.5)
Unknown	0	2 (1.8)	0	2 (0.9)	2 (0.6)
Historical					
Yes	8 (7.5)	5 (4.5)	5 (4.7)	10 (4.6)	18 (5.5)
No	98 (91.6)	102 (91.9)	102 (95.3)	204 (93.6)	302 (92.9)
Unknown	1 (0.9)	4 (3.6)	0	4 (1.8)	5 (1.5)
Elevated CRP (above ULN)[a], n (%)					
Current and/or historical	94 (87.9)	99 (89.2)	94 (87.9)	193 (88.5)	287 (88.3)
Current					
Yes	89 (83.2)	91 (82.0)	81 (75.7)	172 (78.9)	261 (80.3)
No	15 (14.0)	17 (15.3)	22 (20.6)	39 (17.9)	54 (16.6)
Unknown	3 (2.8)	3 (2.7)	4 (3.7)	7 (3.2)	10 (3.1)
Historical					
Yes	88 (82.2)	91 (82.0)	87 (81.3)	178 (81.7)	266 (81.8)
No	12 (11.2)	12 (10.8)	10 (9.3)	22 (10.1)	34 (10.5)
Unknown	7 (6.5)	8 (7.2)	10 (9.3)	18 (8.3)	25 (7.7)
Good response to NSAIDs, n (%)					
Yes	38 (35.5)	33 (29.7)	37 (34.6)	70 (32.1)	108 (33.2)
No	69 (64.5)	78 (70.3)	70 (65.4)	148 (67.9)	217 (66.8)
Unknown	0	0	0	0	0
Family history of axSpA, n (%)					
Yes	15 (14.0)	14 (12.6)	13 (12.1)	27 (12.4)	42 (12.9)
No	87 (81.3)	91 (82.0)	88 (82.2)	179 (82.1)	266 (81.8)
Unknown	5 (4.7)	6 (5.4)	6 (5.6)	12 (5.5)	17 (5.2)

ASAS=Assessment of SpondyloArthritis International Society; axSpA=axial spondyloarthritis; CRP=C-reactive protein; CZP=certolizumab pegol; HLA-B27=human leukocyte antigen B27; MRI=magnetic resonance imaging; NSAIDs=nonsteroidal anti-inflammatory drugs; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; ULN=upper limit of normal

[a] Evaluated in subjects with back pain ≥3 months and onset age <45 years.

Because sacroiliac joint x-ray assessments are associated with considerable radiographic exposure, and screened subjects may not have been randomized into the study, screening x-rays of the sacroiliac joint for definitive diagnosis of AS according to the mNY criteria were considered unnecessary radiographic exposure and were not done in AS001. Instead, reflecting a situation often found in clinical practice in which sacroiliac x-rays are not frequently repeated because structural changes are not expected within months, the most current x-ray prior to screening was used for determination of sacroiliitis and read locally. Of the 178 subjects randomized to the mNY-positive treatment arm (i.e.,

the AS subpopulation), 141 then received Baseline sacroiliac joint x-rays. Of the 147 subjects randomized to the mNY-negative treatment arm (i.e., the nr-axSpA subpopulation), 141 then received Baseline sacroiliac joint x-rays. These Baseline x-rays were assessed via a central reading system utilizing 2 readers, with adjudication by a 3rd reader when the 2 readers did not agree. Of note, many x-rays required adjudication.

The results of the Investigator's screening assessment of sacroiliitis were compared with the Baseline x-ray assessments of sacroiliitis. A total of 20.6% of subjects assessed by the Investigator as having AS at screening based on historical x-rays were considered by the central readers to not have definitive sacroiliitis on Baseline x-ray. A total of 51.1% of subjects assessed by the Investigator as not having AS based on historical x-rays at screening were considered by the central readers to have definitive sacroiliitis on Baseline x-ray. These results highlight the well-known inter-reader variability in diagnosis of definitive sacroiliitis on x-ray which is needed for diagnosis of AS according to mNY criteria. In addition, it suggests that a considerable number of subjects with no clear signs of sacroiliitis in previous x-rays may have progressed to definitive sacroiliitis by the time of the Baseline x-ray, as expected in a population with active disease. To reflect usual clinical practice, the analysis was predefined to be performed primarily according to assessment at Screening based on historic x-ray data.

Concomitant medication

Specific concomitant synthetic DMARDs (sDMARDs) were permitted by the study protocol. Use of any concomitant sDMARD was reported by 32.3% of subjects overall; primarily sulfasalazine (17.2%) and MTX (15.4%). The incidence of concomitant sDMARD use in the AS subpopulation was similar to the overall axSpA population. Use of any concomitant NSAID was reported by 87.7% of subjects in the overall axSpA population; primarily diclofenac/diclofenac sodium (23.4%) and meloxicam (16.3%)

The incidence of concomitant NSAID use in the AS subpopulation was similar to the overall axSpA population. Overall, the treatment groups were well-balanced in concomitant NSAID medication use.

Numbers analysed

At the start of the Double-Blind Treatment Period, 107 subjects were randomized to placebo, 111 subjects to CZP 200mg Q2W sc (starting at Week 6 after 3 doses of 400mg CZP); and 107 to CZP 400mg every 4 weeks (Q4W) sc (starting at Week 8; after 3 doses of 400mg CZP).

A total of 27 placebo subjects escaped to the CZP 200mg Q2W group and 29 placebo subjects escaped to the CZP 400mg Q4W group; these subjects continued to be treated with this dose regimen for the duration of their participation in the study. As of the clinical cut date, all subjects had completed the Double-Blind Treatment Period.

In the Dose-Blind Treatment Period, 41 subjects originally randomized to placebo and not re-randomized to escape treatment at Week 16 were re-randomized in a 1:1 ratio to receive 3 loading doses of CZP 400mg followed by either CZP 200mg Q2W (20 subjects) or CZP 400mg Q4W (21 subjects); all subjects originally randomized to CZP continued to receive the treatment regimen they were assigned at randomization (CZP 200mg Q2W or CZP 400mg Q4W).

A total of 7 subjects did not fulfill the ASAS classification criteria and the data pertaining to these patients were therefore considered as protocol violations.

Outcomes and estimation

Table 3 Summary of hierarchical testing procedure of primary and key secondary efficacy variables (RS, with imputation)

Efficacy variables presented in order of hierarchical testing	p-value	Significant [a]
Step 1: ASAS20 responder rate at Week 12 for CZP 200mg vs PBO	0.004 [b]	Yes
Step 2: ASAS20 responder rate at Week 12 for CZP 400mg vs PBO	<0.001 [b]	Yes
Step 3: ASAS20 responder rate at Week 24 for CZP 200mg vs PBO	<0.001 [b]	Yes
Step 4: ASAS20 responder rate at Week 24 for CZP 400mg vs PBO	<0.001 [b]	Yes
Step 5: Change from Baseline in BASFI at Week 12 for CZP 200mg+400mg vs PBO	<0.001 [c]	Yes
Step 6: Change from Baseline in BASDAI at Week 12 for CZP 200mg+400mg vs PBO	<0.001 [c]	Yes
Step 7: Change from Baseline in BASFI at Week 24 for CZP 200mg+400mg vs PBO	<0.001 [c]	Yes
Step 8: Change from Baseline in BASDAI at Week 24 for CZP 200mg+400mg vs PBO	<0.001 [c]	Yes
Step 9: Change from Baseline in BASMI at Week 12 for CZP 200mg+400mg vs PBO	<0.001 [c]	Yes
Step 10: Change from Baseline in BASMI at Week 24 for CZP 200mg+400mg vs PBO	<0.001 [c]	Yes

ANCOVA=analysis of covariance; ASAS20=Assessment of SpondyloArthritis International Society 20% response criteria; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CZP=certolizumab pegol; PBO=Placebo; RS=Randomized Set; TNFα=tumor necrosis factor alpha

[a] Statistical significance was assessed in the context of the hierarchical testing procedure. Each step was tested at 0.05 two-sided. If the result was not significant at any step, then all steps after that were considered not statistically significant.

[b] p-value was estimated from standard 2-sided Wald asymptomatic test with a 5% alpha level.

[c] p-value was estimated from the ANCOVA model with treatment, region, modified NY criteria (Y/N), and prior anti-TNFα exposure (Y/N) as factors, and Baseline score as a covariate.

Results Primary Endpoint

Table 4 ASAS20 response at Week 12 – primary analysis with Wald test (RS, with imputation)

Week 12	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W+ CZP 400mg Q4W
Overall axSpA population	**N=107**	**N=111**	**N=107**	**N=218**
Responders (%)	38.3	57.7	63.6	60.6
95% CI [a]	(29.1, 47.5)	(48.5, 66.8)	(54.4, 72.7)	(54.1, 67.0)
Difference to PBO [b] (%)	–	19.3	25.2	22.2
95% CI [a]	–	(6.3, 32.4)	(12.3, 38.2)	(11.0, 33.5)
p-value	–	0.004	<0.001	<0.001
AS subpopulation	**N=57**	**N=65**	**N=56**	**N=121**
Responders (%)	36.8	56.9	64.3	60.3
95% CI [a]	(24.3, 49.4)	(44.9, 69.0)	(51.7, 76.8)	(51.6, 69.0)
Difference to PBO [b] (%)	–	20.1	27.4	23.5
95% CI [a]	–	(2.7, 37.5)	(9.7, 45.2)	(8.2, 38.7)
p-value	–	0.026	0.003	0.003
nr-axSpA subpopulation	**N=50**	**N=46**	**N=51**	**N=97**
Responders (%)	40.0	58.7	62.7	60.8
95% CI [a]	(26.4, 53.6)	(44.5, 72.9)	(49.5, 76.0)	(51.1, 70.5)
Difference to PBO [b] (%)	–	18.7	22.7	20.8
95% CI [a]	–	(-1.0, 38.4)	(3.8, 41.7)	(4.1, 37.5)
p-value	–	0.067	0.021	0.017

"–"=not applicable; AS=ankylosing spondylitis; ASAS20=Assessment of SpondyloArthritis International Society 20% response criteria; axSpA=axial spondyloarthritis; CI=confidence interval; CZP=certolizumab pegol; nr-axSpA=nonradiographic axial spondyloarthritis; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set

Note: Nonresponder Imputation (NRI) was used: subjects who withdrew for any reason or placebo subjects who used escape medication were considered nonresponders from the time that they dropped out or when escape therapy was initiated. Subjects who had missing data at a visit were counted as a nonresponder for the respective visit.

[a] Asymptomatic Wald confidence limits.

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

Key secondary endpoints results

Table 5: ASAS20 response at Week 24 (RS, with imputation)

Week 24	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W+ CZP 400mg Q4W
Overall axSpA population	**N=107**	**N=111**	**N=107**	**N=218**
Responders (%)	29.0	66.7	70.1	68.3
95% CI [a]	(20.4, 37.6)	(57.9, 75.4)	(61.4, 78.8)	(62.2, 74.5)
Difference to PBO [b] (%)	–	37.7	41.1	39.4
95% CI [a]	–	(25.4, 50.0)	(28.9, 53.3)	(28.8, 50.0)
p-value	–	<0.001	<0.001	<0.001
AS subpopulation	**N=57**	**N=65**	**N=56**	**N=121**
Responders (%)	33.3	67.7	69.6	68.6
95% CI [a]	(21.1, 45.6)	(56.3, 79.1)	(57.6, 81.7)	(60.3, 76.9)
Difference to PBO [b] (%)	–	34.4	36.3	35.3
95% CI [a]	–	(17.7, 51.1)	(19.1, 53.5)	(20.5, 50.0)
p-value	–	<0.001	<0.001	<0.001
nr-axSpA subpopulation	**N=50**	**N=46**	**N=51**	**N=97**
Responders (%)	24.0	65.2	70.6	68.0
95% CI [a]	(12.2, 35.8)	(51.5, 79.0)	(58.1, 83.1)	(58.8, 77.3)
Difference to PBO [b] (%)	–	41.2	46.6	44.0
95% CI [a]	–	(23.1, 59.4)	(29.4, 63.8)	(29.0, 59.1)
p-value	–	<0.001	<0.001	<0.001

"–"=not applicable; AS=ankylosing spondylitis; ASAS20=Assessment in Axial Spondyloarthritis International Society 20% response criteria; axSpA=axial spondyloarthritis; CI=confidence interval; CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set

Note: Nonresponder Imputation (NRI) was used: subjects who withdrew for any reason or PBO subjects who used escape medication were considered nonresponders from the time that they dropped out or when escape therapy was initiated. Subjects who had missing data at a visit were counted as a nonresponder for the respective visit.

[a] Asymptomatic Wald confidence limits.

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

Table 6 Change from Baseline in BASFI at Weeks 12 and 24 (RS, with imputation)

	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W+ CZP 400mg Q4W
Overall axSpA population	**N=107**	**N=111**	**N=107**	**N=218**
Week 12, LS mean change from Baseline (SE)	-0.53 (0.22)	-2.01 (0.24)	-2.02 (0.24)	-2.02 (0.20)
Week 12, difference to PBO				
LS mean (SE)	–	-1.48 (0.28)	-1.49 (0.28)	-1.49 (0.24)
95% CI	–	(-2.03, -0.94)	(-2.04, -0.94)	(-1.96, -1.01)
p-value	–	<0.001	<0.001	<0.001
Week 24, LS mean change from Baseline (SE)	-0.40 (0.23)	-2.36 (0.25)	-2.20 (0.25)	-2.28 (0.21)
Week 24, difference to PBO				
LS mean (SE)	–	-1.96 (0.29)	-1.80 (0.29)	-1.88 (0.25)
95% CI	–	(-2.53, -1.39)	(-2.38, -1.22)	(-2.38, -1.38)
p-value	–	<0.001	<0.001	<0.001
AS subpopulation	**N=57**	**N=65**	**N=56**	**N=121**
Week 12, LS mean change from Baseline (SE)	-0.58 (0.31)	-1.73 (0.31)	-1.71 (0.34)	-1.72 (0.27)
Week 12, difference to PBO				
LS mean (SE)	–	-1.15 (0.37)	-1.13 (0.39)	-1.14 (0.33)
95% CI	–	(-1.88, -0.42)	(-1.89, -0.36)	(-1.79, -0.49)
p-value	–	0.002	0.004	<0.001
Week 24, LS mean change from Baseline (SE)	-0.74 (0.32)	-2.36 (0.33)	-2.29 (0.35)	-2.32 (0.28)
Week 24, difference to PBO				
LS mean (SE)	–	-1.62 (0.38)	-1.55 (0.40)	-1.58 (0.34)
95% CI	–	(-2.38, -0.86)	(-2.34, -0.75)	(-2.26, -0.91)
p-value	–	<0.001	<0.001	<0.001

	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W+ CZP 400mg Q4W
nr-axSpA subpopulation	**N=50**	**N=46**	**N=51**	**N=97**
Week 12, LS mean change from Baseline (SE)	-0.40 (0.35)	-2.29 (0.40)	-2.26 (0.40)	-2.28 (0.34)
Week 12, difference to PBO				
LS mean (SE)	–	-1.89 (0.42)	-1.86 (0.42)	-1.87 (0.37)
95% CI	–	(-2.73, -1.05)	(-2.68, -1.03)	(-2.59, -1.15)
p-value	–	<0.001	<0.001	<0.001
Week 24, LS mean change from Baseline (SE)	0.00 (0.37)	-2.40 (0.42)	-2.07 (0.43)	-2.24 (0.36)
Week 24, difference to PBO				
LS mean (SE)	–	-2.40 (0.45)	-2.07 (0.44)	-2.23 (0.39)
95% CI	–	(-3.29, -1.51)	(-2.95, -1.19)	(-3.00, -1.47)
p-value	–	<0.001	<0.001	<0.001

"–"=not applicable; ANCOVA=analysis of covariance; AS=ankylosing spondylitis; axSpA=axial spondyloarthritis; nr-axSpA=nonradiographic axial spondyloarthritis; BASFI=Bath Ankylosing Spondylitis Functional Index; CI=confidence interval; CZP=certolizumab pegol; LS=least squares; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; SE=standard error; TNFα=tumor necrosis factor alpha

Note: Last observation carried forward (LOCF) was used: for subjects who withdrew for any reason or subjects with a missing Week 12/24 measurement, last observation prior to the early withdrawal or Week 12/24 was carried forward to Week 12/24.

Note: ANCOVA model with treatment, region, and prior anti-TNFα exposure (yes/no) as factors, and Baseline score as a covariate.

Table 7 Change from Baseline in BASDAI at Weeks 12 and 24 (RS, with imputation)

	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W+ CZP 400mg Q4W
Overall axSpA population	**N=107**	**N=111**	**N=107**	**N=218**
Week 12, LS mean change from Baseline (SE)	-1.22 (0.22)	-2.82 (0.24)	-2.80 (0.24)	-2.81 (0.20)
Week 12, difference to PBO				
LS mean (SE)	–	-1.61 (0.28)	-1.59 (0.28)	-1.60 (0.24)
95% CI	–	(-2.15, -1.06)	(-2.14, -1.04)	(-2.07, -1.12)
p-value	–	<0.001	<0.001	<0.001
Week 24, LS mean change from Baseline (SE)	-1.05 (0.23)	-3.08 (0.25)	-3.01 (0.25)	-3.05 (0.20)
Week 24, difference to PBO				
LS mean (SE)	–	-2.03 (0.29)	-1.96 (0.29)	-1.99 (0.25)
95% CI	–	(-2.59, -1.47)	(-2.53, -1.39)	(-2.49, -1.50)
p-value	–	<0.001	<0.001	<0.001
AS subpopulation	**N=57**	**N=65**	**N=56**	**N=121**
Week 12, LS mean change from Baseline (SE)	-1.02 (0.30)	-2.51 (0.31)	-2.43 (0.33)	-2.47 (0.26)
Week 12, difference to PBO				
LS mean (SE)	–	-1.49 (0.36)	-1.40 (0.36)	-1.45 (0.32)
95% CI	–	(-2.20, -0.78)	(-2.15, -0.66)	(-2.08, -0.81)
p-value	–	<0.001	<0.001	<0.001
Week 24, LS mean change from Baseline (SE)	-1.13 (0.30)	-3.00 (0.30)	-2.98 (0.33)	-2.99 (0.26)
Week 24, difference to PBO				
LS mean (SE)	–	-1.87 (0.36)	-1.85 (0.37)	-1.86 (0.32)
95% CI	–	(-2.57, -1.16)	(-2.59, -1.11)	(-2.49, -1.23)
p-value	–	<0.001	<0.001	<0.001

	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W+ CZP 400mg Q4W
nr-axSpA subpopulation	**N=50**	**N=46**	**N=51**	**N=97**
Week 12, LS mean (SE)	-1.52 (0.36)	-3.31 (0.42)	-3.40 (0.43)	-3.36 (0.36)
Week 12, difference to PBO				
LS mean (SE)	–	-1.79 (0.44)	-1.88 (0.44)	-1.84 (0.38)
95% CI	–	(-2.66, -0.92)	(-2.74, -1.02)	(-2.59, -1.08)
p-value	–	<0.001	<0.001	<0.001
Week 24, LS mean (SE)	-1.01 (0.39)	-3.27 (0.45)	-3.16 (0.46)	-3.21 (0.39)
Week 24, difference to PBO				
LS mean (SE)	–	-2.26 (0.47)	-2.15 (0.47)	-2.21 (0.41)
95% CI	–	(-3.20, -1.33)	(-3.07, -1.22)	(-3.01, -1.40)
p-value	–	<0.001	<0.001	<0.001

"–"=not applicable; ANCOVA=analysis of covariance; AS=ankylosing spondylitis; axSpA=axial spondyloarthritis; nr-axSpA=nonradiographic axial spondyloarthritis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; CI=confidence interval; CZP=certolizumab pegol; LS=least square; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; SE=standard error; TNFα=tumor necrosis factor alpha

Note: Last observation carried forward (LOCF) was used: for subjects who withdrew for any reason or subjects with a missing Week 12/24 measurement, last observation prior to the early withdrawal or Week 12/24 was carried forward to Week 12/24.

Note: ANCOVA model with treatment, region, modified NY criteria (yes/no) and prior anti-TNFα exposure (yes/no) as factors and Baseline score as covariate.

Table 8 Change from Baseline in CRP (FAS, with imputation), SPARCC scores, and ASspiMRI-a scores (MRIS, OC)

Overall axSpA population	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W+400mg Q4W
CRP levels	**N=106**	**N=111**	**N=107**	**N=218**
Week 12, mean change from Baseline (SD)	-2.39 (19.75)	-11.34 (19.28)	-10.49 (15.43)	-10.92 (17.46)
Week 12, difference to PBO[a]				
LS mean (SE)	–	-10.95 (1.88)	-10.40 (1.90)	-10.67 (1.64)
95% CI	–	(-14.63, -7.26)	(-14.13, -6.67)	(-13.90, -7.44)
p-value	–	<0.001	<0.001	<0.001
Week 24, mean change from Baseline (SD)	-2.29 (20.41)	-11.99 (19.98)	-9.83 (14.49)	-10.93 (17.50)
Week 24, difference to PBO[a]				
LS mean (SE)	–	-11.97 (1.62)	-10.13 (1.64)	-11.05 (1.42)
95% CI	–	(-15.16, -8.78)	(-13.36, -6.91)	(-13.84, -8.26)
p-value	–	<0.001	<0.001	<0.001
SPARCC scores – sacroiliac joint	**N=50**	**N=49**	**N=54**	**N=103**
Baseline, mean (SD)	17.10 (17.81)	10.05 (12.67)	11.31 (12.94)	10.71 (12.76)
Week 12, LS mean change from Baseline (SE)	0.35 (1.04)	-4.58 (1.16)	-5.81 (1.13)	-5.20 (0.95)
Week 12, difference to PBO[b]				
LS mean (SE)	–	-4.93 (1.36)	-6.16 (1.33)	-5.54 (1.19)
95% CI	–	(-7.63, -2.24)	(-8.79, -3.52)	(-7.90, -3.19)
p-value	–	<0.001	<0.001	<0.001

Overall axSpA population	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W+400mg Q4W
ASspiMRI-a scores - spine	**N=50**	**N=49**	**N=54**	**N=103**
Baseline, mean (SD)	5.38 (7.36)	5.97 (7.08)	3.79 (4.98)	4.82 (6.14)
Week 12, LS mean change from Baseline (SE)	1.23 (0.58)	-2.03 (0.65)	-1.52 (0.65)	-1.78 (0.54)
Week 12, difference to PBO[b]				
LS mean (SE)	–	-3.26 (0.76)	-2.75 (0.74)	-3.00 (0.65)
95% CI	–	(-4.75, -1.76)	(-4.22, -1.28)	(-4.29, -1.71)
p-value	–	<0.001	<0.001	<0.001

"–"=not applicable; ANCOVA=analysis of covariance; ASspiMRI-a=ankylosing spondylitis spine magnetic resonance imaging scoring system for disease activity; axSpA=axial spondyloarthritis; CI=confidence interval; CRP=C-reactive protein; CZP=certolizumab pegol; FAS=Full Analysis Set; LS=least square; MRIS=Magnetic Resonance Imaging Set; OC=observed case; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation; SE=standard error; SPARCC=SpondyloArthritis Research Consortium of Canada; TNFα=tumor necrosis factor alpha

[a] ANCOVA model with treatment, region, modified NY criteria (yes/no) and prior anti-TNFα exposure (yes/no) as factors

[b] ANCOVA model with treatment, region and prior anti-TNFα exposure (yes/no) as factors and Baseline score as covariate

In the nr-axSpA subpopulation, the LS mean change from Baseline in sacroiliac joint SPARCC scores at Week 12 was greater in the CZP 200mg Q2W+CZP 400mg Q4W group (-4.02 points) compared with the placebo group (2.69 points); the difference to placebo was -6.71 (p<0.001; Pearson's coefficient of correlation in actual scores between readers: 0.788).

Also, the LS mean change from Baseline in spine ASspiMRI-a scores at Week 12 was greater in the CZP 200mg Q2W+CZP 400mg Q4W group (-1.48 points) compared with the placebo group (0.65 points); the difference to placebo was -2.13 (p=0.017; Pearson's coefficient of correlation in actual scores

between readers: 0.840 [AS001 Week 24]). For both subpopulations, as with the overall axSpA population, the active treatment groups showed a decrease in spine ASspiMRI-a scores from Baseline, whereas the placebo groups slightly increased from Baseline. No clinically meaningful differences were observed between CZP treatment groups.

Caution must be taken when interpreting the subpopulation results due to small sample sizes; however, in general, these results suggest sacroiliac joint lesion improvement as measured by MRI with CZP treatment in subjects with active axSpA including AS.

Table 9 ASAS40 response at Weeks 12 and 24 (FAS, with imputation)

	PBO[a]	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W+ CZP 400mg Q4W
Overall axSpA population	**N=106**	**N=111**	**N=107**	**N=218**
Week 12 responders (%)	19 (17.9)	48 (43.2)	52 (48.6)	100 (45.9)
Difference to PBO [b] (%)	–	25.3	30.7	27.9
95% CI	–	(13.6, 37.1)	(18.7, 42.6)	(18.1, 37.8)
p-value	–	<0.001	<0.001	<0.001
Week 24 responders (%)	16 (15.1)	57 (51.4)	56 (52.3)	113 (51.8)
Difference to PBO [b] (%)	–	36.3	37.2	36.7
95% CI	–	(24.7, 47.8)	(25.6, 48.9)	(27.2, 46.3)
p-value	–	<0.001	<0.001	<0.001
AS subpopulation	**N=57**	**N=65**	**N=56**	**N=121**
Week 12 responders (%)	11 (19.3)	26 (40.0)	28 (50.0)	54 (44.6)
Difference to PBO [b] (%)	–	20.7	30.7	25.3
95% CI	–	(5.0, 36.4)	(14.1, 47.3)	(11.8, 38.9)
p-value		0.011	<0.001	<0.001
Week 24 responders (%)	9 (15.8)	31 (47.7)	33 (58.9)	64 (52.9)
Difference to PBO [b] (%)	–	31.9	43.1	37.1
95% CI	–	(16.5, 47.3)	(27.2, 59.1)	(24.1, 50.1)
p-value	–	<0.001	<0.001	<0.001
nr-axSpA subpopulation	**N=49**	**N=46**	**N=51**	**N=97**
Week 12 responders (%)	8 (16.3)	22 (47.8)	24 (47.1)	46 (47.4)
Difference to PBO [b] (%)	–	31.5	30.7	31.1
95% CI	–	(13.7, 49.3)	13.6, 47.9)	(16.7, 45.4)
p-value	–	<0.001	<0.001	<0.001
Week 24 responders (%)	7 (14.3)	26 (56.5)	23 (45.1)	49 (50.5)
Difference to PBO [b] (%)	–	42.2	30.8	36.2
95% CI	–	(24.9, 59.6)	(14.0, 47.6)	(22.3, 50.2)
p-value	–	<0.001	<0.001	<0.001

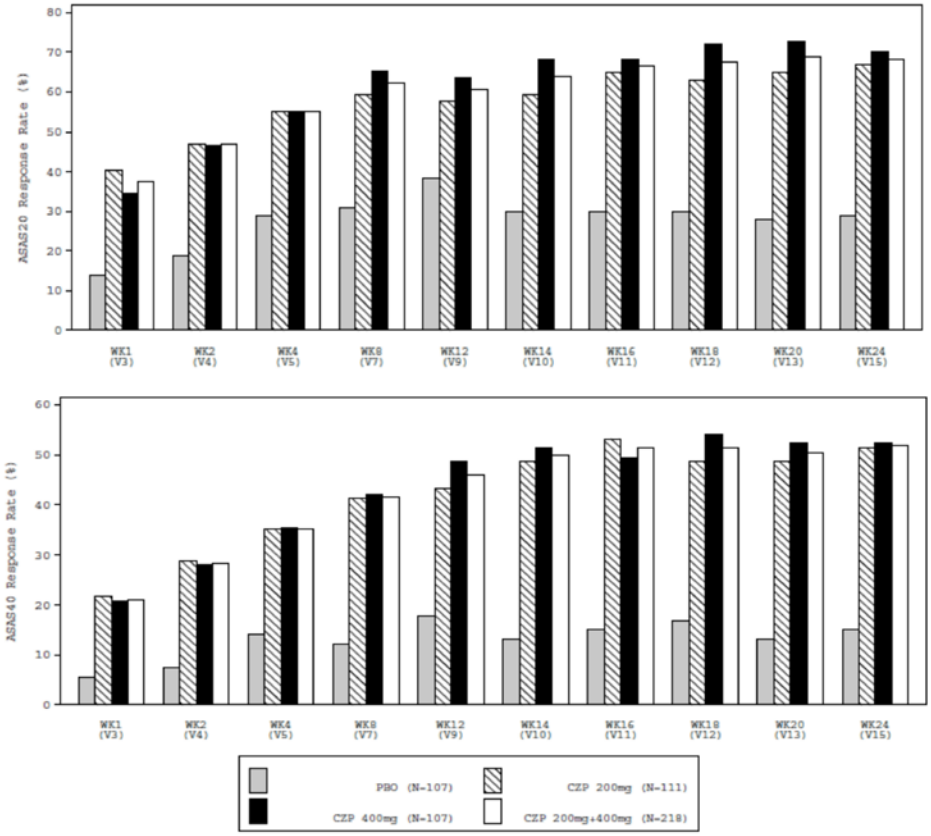
"–"=not applicable; AS=ankylosing spondylitis; ASAS40= Assessment of SpondyloArthritis International Society 40% response criteria; axSpA=axial spondyloarthritis; CI=confidence interval; CZP=certolizumab pegol; FAS=Full Analysis Set; nr-axSpA=nonradiographic axSpA; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks

Note: Nonresponder Imputation (NRI) was used: subjects who withdrew for any reason or PBO subjects who used escape medication were considered nonresponders from the time that they dropped out or when escape therapy was initiated. Subjects who had missing data at a visit were counted as a nonresponder for the respective visit.

[a] For the entire placebo group, NRI were used for subjects escaping to CZP.

[b] Treatment difference: CZP 200mg Q2W – PBO, CZP 400mg Q4W – PBO, and CZP 200mg Q2W+ CZP 400mg Q4W PBO (and corresponding 95% CI and p value) were estimated using a standard 2-sided Wald asymptotic test with a 5% alpha level. The corresponding 95% CIs for the differences were constructed using their asymptotic standard errors (asymptomatic Wald confidence limits).

Figure 6 ASAS20 and ASAS40 response by visit (RS with imputation)



ASAS20=Assessment in Axial SpondyloArthritis International Society 20% response criteria; ASAS40=Assessment in Axial SpondyloArthritis International Society 40% response criteria; CZP=certolizumab pegol; PBO=placebo; RS=Randomized Set; V=visit; wk=week. Data sources: AS001 Week 24 CSR Figure 8-1; AS001 Week 24 CSR Figure 8.2.

Table 10: ASAS50, and ASAS70 Responder Rate at 12 Weeks Population: Full Analysis Set [Imputation]

Response Criteria	PBO Through-out the DB N=51 n (%)	PBO escaping to CZP 200mg N=27 n (%) [a]	PBO escaping to CZP 400mg N=28 n (%) [a]	PBO N=106 n (%) [b]	CZP 200mg N=111 n (%)	CZP 400mg N=107 n (%)	CZP 200mg+ 400mg N=218 n (%)	CZP 200mg - PBO % (95% CI) p-value [c]	CZP 400mg - PBO % (95% CI) p-value [c]	CZP 200mg+400mg -PBO % (95% CI) p-value [c]
ASAS50	14 (27.5)	1 (3.7)	0	15 (14.2)	43 (38.7)	46 (43.0)	89 (40.8)	24.6 (13.4,35.8) <.001	28.8 (17.3,40.3) <.001	26.7 (17.4,36.0) <.001
ASAS70	2 (3.9)	0	0	2 (1.9)	27 (24.3)	26 (24.3)	53 (24.3)	22.4 (14.0,30.8) <.001	22.4 (13.9,30.9) <.001	22.4 (16.2,28.7) <.001

At Week 12, the percentage of subjects with an ASAS5/6 response was greater in the CZP 200mg Q2W+CZP 400mg Q4W group (43.1%) compared with the placebo group (8.5%; Table 8-10); the difference to placebo was 34.6% (p<0.001). The treatment effect continued to Week 24.

Nocturnal back pain was improved in CZP-treated subjects in the overall axSpA population atWeek 12. The mean change from Baseline at Week 12 was greater in the CZP 200mgQ2W+CZP 400mg Q4W group (-3.20 points) compared with placebo (-1.38 points) the difference to placebo was -1.84 points (p<0.001).

Clinically meaningful BASDAI50 response rates were seen at Week 12 in the CZP 200mg Q2W+CZP 400mg Q4W group 44.5% compared with the placebo group (13.2%) the difference to placebo was

31.3% (p<0.001). This effect was seen also at Week 24, with higher response rates in the CZP 200mg Q2W+ CZP 400mg Q4W group (52.3%) compared with the placebo group (17.9%); the difference to placebo was 34.4% (p<0.001).

Supportive secondary endpoints

Supportive efficacy endpoints assessed in the AS001 study demonstrated the effect of CZP on several components of active axial spondyloarthritis.

Spinal mobility (BASMI)

Spinal mobility was assessed by BASMI at Baseline, Week 12 and Week 24. Clinically meaningful and statistically significant differences in Cimzia-treated patients compared with placebo-treated patients were demonstrated at each post-baseline visit. The difference from placebo tended to be greater in nr-axSpA than in the AS subpopulation which may be due to less chronic structural damage in nr-axSpA patients.

Impact of certolizumab pegol on physical function, pain, fatigue and sleep

CZP-treated subjects showed significant improvements in physical function (BASFI), relief of pain Total and Nocturnal Back Pain NRS), and fatigue (BASDAI-fatigue item) by Week 1 which were maintained to Week 24. Clinically relevant changes from Baseline in both domains of the MOS Sleep Scale were seen in both CZP groups relative to the placebo group by Week 4 which were maintained through Week 24. These improvements in physical function, pain, fatigue and sleep were sustained up to Week 48.

Impact of certolizumab pegol on health related quality of life (SF-36 and ASQoL)

Health-related quality of life was assessed via the SF-36 and the ASQoL (a disease-specific measure of HRQoL). Health-related quality of life was notably improved in CZP-treated subjects compared with placebo-treated subjects. Improvements were also demonstrated in the ASQoL following CZP treatment in the overall axSpA population.

Cimzia-treated patients reported significant improvements in axial spondyloarthritis-related productivity at work and within household, as reported by the Work Productivity Survey as compared to placebo. These improvements were sustained up to Week 48.

Ancillary analyses

The ASAS20 response in the overall axSpA population as well as the 2 subpopulations at Week 12 was analyzed by subgroups of age, gender, race, symptom duration, anti-CZP antibody status, and Baseline CRP category. Of note, more males were ASAS20 responders compared with females in the overall axSpA population only at Week 12. In the overall axSpA population, a higher rate of ASAS20 responders was seen in the placebo group in Latin America at Week 12 (less at Week 24). For anti-CZP antibody status, race, region (in subpopulations), anti-TNFα prior exposure, and duration of disease, no meaningful conclusions can be drawn due to the small number of subjects in at least 1 of the treatment categories.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study AS001

The clinical development program for CZP in subjects with axSpA included a single pivotal Phase 3 study, Study AS001. This is an on-going, multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study to evaluate the efficacy and safety of CZP in adult subjects with active axSpA (including AS). The study was designed to support the demonstration of efficacy in improving the signs and symptoms, measures of inflammation on imaging, physical function and workplace and household productivity, and quality of life in the studied population. Study AS001 was ongoing at the time of submission of this application. A data cut-off of 31 May 2012 was used for this submission. Interim data from this study covering the 24 weeks double blind treatment period form the basis for all efficacy data to support the claimed indication. As of the data cut-off date, 325 were analysed; 111 subjects in the CZP 200mg Q2W group, 107 subjects in the CZP 400mg Q4W group, and 107 in the placebo group.

The objective was to demonstrate the efficacy of CZP 200mg Q2W and CZP 400mg Q4W after a loading dose of CZP 400mg at Weeks 0, 2, and 4 on the signs and symptoms of active axSpA. The main inclusion criteria were:

- Adult onset axSpA of at least 3 months symptom duration. Half of subjects who met the ASAS criteria should not have fulfilled the mNY criteria for definite diagnosis of AS.
- Active disease as defined by BASDAI score ≥4, spinal pain ≥4 on a 0 to 10 Numerical Rating Scale and objective signs of inflammation: C-reactive protein (CRP) > upper limit of normal and/or current evidence for sacroiliitis on MRI as defined by ASAS classification criteria
- Intolerance or inadequate response to at least 1 NSAID, defined as lack of response to at least 30 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID or lack of response to treatment with at least 2 NSAIDs at the maximum tolerated dose for 2 weeks each.

The study includes 5 study periods: Screening, the Double-Blind Treatment Period (up to Week 24), the Dose-Blind Treatment Period (Week 24 to Week 48), the Open-Label Period (Week 48 to Week 204), and the Safety Follow-Up Period (Week 204 to Week 212). The Screening Period and the Double-Blind Treatment Period (up to Week 24; DB1) were completed and, together with additional clinical safety data after the DB1 lock to 31 May 2012, form the basis of this submission.

The design of the study is endorsed. In the guideline on clinical investigation of medicinal products for the treatment of AS, the primary endpoint, ASAS20 is stated to be an acceptable efficacy endpoint for some products, e.g. NSAIDS. It is also stated that in the case of products belonging to other therapeutic classes a higher improvement may be required i.e. ASAS40. The primary endpoint, ASAS20 is relatively modest for a TNF-blocker, but ASAS 40, was also measured as a secondary endpoint and presented; this is therefore considered satisfactory.

The study was designed to enrol an equal number of AS and nr-axSpA patients, to allow comparison between axSpA subgroups. However, since sacroiliac x-ray was performed at baseline, after stratification was already made, the subgroups seemed to have been mixed, as it appeared that 20% of the subjects, earlier assessed as AS, lacked changes consistent with this diagnosis according to the central readers, and of the subjects locally assessed as nr-axSpA, more than 50% were considered to have radiological changes by the central readers. The latter may mirror progress of the disease, since

the earlier assessments may have been made on investigations performed long time ago. The information obtained from baseline investigations on what sub-group (nr-axSpA or AS) the subjects belonged to appeared to have been neglected. The result would be that a number of subjects in the nr-axSpA subgroup fulfil in reality AS criteria and vice versa. Thus, any subgroup analysis addressing the nraAxSpA and AS cohorts may be of limited value. During the procedure, the MAH discussed the impact of the initial "misclassification" on the presented subgroup analyses, and also provided post hoc analyses based on central reading of baseline x-rays. ASAS 20 at 12 and 24 weeks, as well as BASFI, BASDAI and BASMI data at week 12 and 24 were recalculated. At Week 12, the difference to placebo in ASAS20 response was 19.0% in the CZP treated AS subpopulation, and 24.4% in the nr-axSpA subpopulation. The corresponding figures for the original analysis were 23.5% in the CZP treated AS subpopulation, and 22.2% in the nr-axSpA subpopulation. At Week 24, the difference to placebo in ASAS20 response was 37.7% in the CZP treated AS subpopulation, and 40.0% in the nr-axSpA subpopulation. The corresponding figures for the original analysis were 35.3% in the CZP treated AS subpopulation, and 44.0% in the nr-axSpA subpopulation. All results for BASFI, BASMI and BASDAI at weeks 12 and 24 using patient assignment based on centrally read baseline x-rays showed statistically significant difference to placebo for the combined CZP group with significance for both the AS and the nr-axSpA group. Overall, these results did not change the initial interpretation of the positive outcome.

Efficacy data and additional analyses

The primary efficacy endpoint in AS001 was ASAS20 response at Week 12. The key secondary efficacy variables were ASAS20 response at Week 24, change from Baseline in BASFI at Week 12 and Week 24, change from Baseline in BASDAI at Weeks 12 and Week 24, change from Baseline in BASMI at Weeks 12 and Week 24, change from Baseline in spine ASspiMRI-a to Week 12, and change from Baseline in sacroiliac SPARCC scores to Week 12. The primary analyses of the efficacy variables were performed for the RS with imputation of missing values. A hierarchical test procedure was applied for the analysis of the primary and key secondary efficacy endpoints to protect the overall significance level for the multiplicity of dose groups and endpoints.

At Baseline, subjects in AS001 reported significant disease burden as demonstrated by mean BASDAI scores of 6.44, BASFI scores of 5.38, and BASMI scores of 3.84. Mean spinal pain at Baseline (total back pain NRS) was 7.02 on a 0 to 10 NRS.

The primary efficacy endpoint in AS001 was met. The ASAS20 response at Week 12 was statistically significantly greater ($p<0.004$ and $p<0.001$) in both active groups (CZP 200mg Q2W [57.7%] and CZP 400mg Q4W [63.6%]) compared with the placebo group (38.3%), and the differences to placebo (19.3% in the 200mg Q2W group and 25.2% in the Q4W group) are clinically relevant.

The change from Baseline in key secondary efficacy endpoints supports the primary efficacy endpoint. The analyses of change from Baseline in BASFI, BASDAI, and BASMI linear at Weeks 12 and 24 were clinically meaningful, and the CZP-treated groups differed statistically significantly from placebo.

The secondary endpoint ASAS40 was also met for both dosing groups, with a difference to placebo of approximately 30% at week 12 and slightly higher at week 24.

The originally submitted overall efficacy analysis was convincing. Further information on the imputation of missing values and some additional sensitivity analyses were provided during the procedure and considered satisfactory.

It is noted that the subgroup analyses showed that the ASAS 20 response rates of female subjects, patients with AS of ≥ 45 years, were not significant as compared to placebo at week 12. This has been discussed by the MAH and after 12 weeks the difference to placebo was significant. ASAS40 response

was statistically significant compared to placebo at Week 12 and Week 24. This was reflected in section 5.1 of the SmPC.

Looking at the subpopulations AS and nr-axSpA, the difference to placebo in ASAS20 response was 20.1% in the 200mgQ2W group and 27.2% in the 400mgQ4W in the AS subpopulation, and 18.7% and 22.7% respectively in the nr-axSpA subpopulation. Since there were uncertainties regarding the conformity of the subpopulations as discussed above, these figures are uncertain. However the CHMP considered unlikely that the effect results in the nr-axSpA population were driven mainly by responders in the AS sub-group.

The week 24 results showed efficacy of CZP for the overall AxSpA population in both treatment groups. The difference to placebo for ASAS20 was 37.7% and 41.1% in the 200mg Q2W and 400mg Q2W groups respectively. In both subpopulations, approximately two thirds of the subjects achieved ASAS20 response.

During the procedure it was clarified that there is no clinically meaningful difference between the two treatment regimens with respect to efficacy in AS001, as observed numerical differences between CZP 200mg Q2W and CZP 400mg Q4W were not consistent across endpoints and treatment groups, were within the 95% CI of one another.

Inflammation in the overall axSpA population

The LS mean change from Baseline in the MRI set was greater in the CZP 200mg Q2W+CZP 400mg Q4W group (-5.20) compared with the placebo group (0.35 points); the difference to placebo was -5.54. (-4.93 in the 200 mg 2QW and -6.16 in the 400 mg 4QW, respectively). The mean baseline values were 17.10 in the placebo group, and 10.05 and 11.31 in the 200mg2QW and 400mg Q4W respectively. Thus, a Baseline imbalance was noted. The analysis of change from Baseline in SPARCC scores was adjusted for Baseline values.

Also when ASspiMRI scores were used, there was a difference to placebo after 12 weeks in the CZP-treated groups (-3.26 in the 200mg2QW and -2.75 in the 400mg 4QW respectively). The mean baseline values were 5.38 in the placebo group, and 5.97 and 3.79 in the 200mg2QW and 400mg Q4W respectively.

The decrease of sacroiliac inflammation measured either by SPARCC score of ASspiMRI-a score, is considered clinically relevant.

MRI investigation was only performed in 153 patients, as a substudy. Nevertheless, results also in this subgroup convincingly show a reduction of SPARCC scores (see Table 8), which support a relevant effect on inflammation.

In the overall axSpA population as well as in the different dosing groups and diagnostic subgroups, a clinically meaningful decrease in CRP levels from Baseline was seen at Weeks 12 and 24 in the CZP groups.

AxSpA, spondyloarthritis with predominantly axial involvement, is a chronic inflammatory rheumatic disease. It comprises the disease subgroup AS, as well as a disease subgroup characterized by little or no changes on plain radiographs of the sacroiliac joints, referred to as nr-axSpA. The modified New York criteria (mNY) for classification of AS are often used to diagnose AS. The mNY criteria require clear evidence of definite sacroiliitis on conventional radiography. Patients with axSpA, including AS and nr-axSpA, can now be classified by the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axSpA. The ASAS classification criteria for axSpA require the presence of chronic back pain for more than 3 months with an onset before 45 years of age, either the presence of sacroiliitis on radiographs or MRI, plus at least 1 clinical spondyloarthritis parameter (“imaging

arm") or the presence of HLA-B27 plus at least 2 clinical spondyloarthritis parameters ("clinical arm"). Thus, the ASAS classification criteria allows classification of axSpA in the absence of any imaging evidence of sacroiliitis, provided HLA B-27 is present together with 2 clinical parameters (i.e., nr-axSpA).

The MAH initially applied for the following indication wording:

"Axial spondyloarthritis

Cimzia is indicated for the treatment of adult patients with active axial spondyloarthritis, including patients with ankylosing spondylitis and patients with non-radiographic axial spondyloarthritis who have had an inadequate response to NSAIDs."

The first line treatment of patients with AxSpA is NSAID, but when these are not tolerated or provide an inadequate response, a TNF-blocker, adalimumab, recently received in July 2012 an approval for the indication for treatment of patients with objective signs of inflammation by elevated CRP and/or MRI for nr-axial Spondyloarthritis. The MAH for Cimzia did not include any measures for objective signs of inflammation in the originally proposed indication. This was not accepted, since no classification criteria have a 100% positive specificity, and a small proportion of patients meeting clinical criteria will have non inflammatory back pain. Given the high prevalence of non-inflammatory back pain in the general population, the total numbers of over treated patients in a clinical setting may be unacceptable unless objective signs of inflammation are requested. Further, it should be noted, that the study was designed to include only patients with objective signs of inflammation, and the target population of the indication should mirror the studied population. The MAH was therefore requested to provide a revised indication wording, taking the above discussion into account. It was proposed that this wording should follow the same structure as that of adalimumab, with a global heading of AxSpA followed by AS and nr-AxSpA as subheadings. The CHMP also requested to add the word "severe" was requested to be added to the indication wording in order to better reflect the population studied as measured by BASDAI and Pain VAS/NRI values. Also for completeness it was requested to add "intolerance to NSAID" as criteria to receive the treatment in addition to the criteria of "inadequate response to NSAID". These changes were accepted by the MAH.

The final wording of the indication as proposed by the MAH and agreed by the CHMP reads as follows:

Axial spondyloarthritis

Cimzia is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising:

Ankylosing spondylitis (AS)

Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Axial spondyloarthritis without radiographic evidence of AS

Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to NSAIDs.

As described in the RMP the MAH will submit the final results of Study AS001 by Q2 2016 which will bring additional data to further characterize the long term benefit of CZP treatment in axial spondyloarthritis patients up to 204 weeks of treatment.

There is very limited knowledge on how long treatment should be continued in subjects in whom there is no disease activity following treatment, or the efficacy and safety of retreatment after disease flare. In order to address this, the MAH will conduct a double-blind, parallel-group, placebo controlled, randomized withdrawal study addressing both withdrawal and dose reduction, in subjects with early

AxSpA. The objective of this study is to evaluate whether a subject in no or low disease activity will remain in no or low disease activity following withdrawal or dose reduction of CZP. The proposed study is divided into two phases. The first phase is an open-label run-in phase where subjects will be given CZP at the approved dose. In the second phase of the study, subjects achieving no or low disease activity at two consecutive visits will be eligible to enter the randomized, double-blind part of the study and will receive either a full dose of CZP, a half dose of CZP or placebo for 48 weeks. Subjects in the half dose of CZP or full withdrawal arm who experience a flare (i.e. loss of no or low disease activity) during the double blind randomized phase subjects will be offered to escape to full dose of CZP for at least 12 weeks. Subjects not meeting the criteria for randomization after the run in phase will be treated outside of this study at the discretion of the investigator. This study will provide information about the proportion of subjects with early axSpA and who maintain their low disease activity state for an additional 48 weeks following drug withdrawal or dose reduction. The study will also collect information on efficacy and safety of re-treatment. Approximately 500 to 800 subjects are expected to be enrolled into the open label phase. The MAH will provide the results of this study by January 2019 as described in the RMP.

2.4.3. Conclusions on the clinical efficacy

Study AS001 has provided results that support efficacy of both dosing groups of CZP in the overall AxSpA population, both with respect to symptoms, spinal mobility and inflammation. The overall efficacy analysis was convincing. Further information on the imputation data and some additional sensitivity analyses were presented during the procedure. The analysis of the 2 diagnostic subgroups, AS and nr-axSpA, shows a similar effect in both groups. Although there is an uncertainty regarding the conformity of these groups, the results are considered sufficiently reliable.

In AS001 clinical trial, 200 mg Q2W and 400 mg Q4W was tested in comparison to placebo during a 24 week period. The primary efficacy endpoint, the ASAS20 response at Week 12 was statistically significantly greater ($p<0.004$ and $p<0.001$) in both active groups (CZP 200mg Q2W [57.7%] and CZP 400mg Q4W [63.6%]) compared with the placebo group (38.3%). The differences to placebo (19.3% in the 200mg Q2W group and 25.2% in the Q4W group) are clinically relevant. Further, also the secondary endpoint ASAS40, which is considered more relevant for an anti-TNF agent, was met for both dosing groups, with a difference to placebo of approximately 30% at week 12 and slightly higher at week 24.

Other secondary analyses also supported efficacy. Similar results were achieved in both the AS and nr-axSpA subpopulations. Although female patients showed ASAS20 responses at Week 12, statistical significance versus placebo was observed beyond Week 12. However, ASAS40 response was statistically significant compared to placebo at Week 12 and Week 24.

Clinically meaningful and statistically significant differences in Cimzia-treated patients compared to placebo were observed on spinal mobility as assessed by BASMI at Baseline, Week 12 and Week 24. Patients reported significant improvements in physical function, in pain, in tiredness, quality of life and productivity compared to placebo. Significant inhibition of inflammatory signs in both sacroiliac joints and the spine was observed in the Cimzia-treated patient (all doses group), in the overall axial spondyloarthritis population as well as in the sub-populations of AS and nr-axSpA.

During the procedure the CHMP questioned the wording of the proposed indication that did not include measures for objective signs of inflammation. As the pivotal study was designed to include only patients with objective signs of inflammation (to reduce the risk of treating patients with chronic non inflammatory back pain erroneously classified as nraAxSpA), the CHMP required the indication to include measures for objective signs of inflammation, in the form of elevated CRP or positive MRI findings in sacroiliac joints. The CHMP also required that the indication covers only “severe” disease in

order to reflect the population studied as measured by BASDAI and Pain VAS/NRI values and is structured with a global heading of AxSpA followed by subheadings for AS and nr-AxSpA in line with an already authorised product. Overall the CHMP agreed with the final wording of the indication implementing the above-required changes.

As described in the RMP the MAH will submit the final results of Study AS001 by Q2 2016 which will bring additional data to further characterize the long term benefit of CZP treatment in axial spondyloarthritis patients up to 204 weeks of treatment. As there is very limited knowledge on how long treatment should be continued in subjects in whom there is no disease activity following treatment, or the efficacy (and safety) of retreatment after disease flare. In addition, the MAH will conduct a blinded withdrawal trial that will provide information on how long treatment should be continued in responders; what proportion of patients treated early in their disease achieve remission and also provide data on the efficacy and safety of re-treatment. The study protocol of this study should be approved by the CHMP before the study can start. Results of this study are expected in January 2019.

The CHMP considers the following measures necessary to address issues related to efficacy:

- Study AS001: Phase 3, multicenter, randomized, double blind, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in subjects with active axial spondyloarthritis (axial SpA)

- Remission/withdrawal study in early axial spondyloarthritis

2.5. Clinical safety

2.5.1. Introduction

Safety data were evaluated from the ongoing AS001 study, which includes data from the completed Double-Blind Treatment Period as well as pooled data from completed visits in the other study periods through a clinical data cutoff date of 31 May 2012 (All CZP Safety Pool).

For the Double-Blind Treatment Period, safety variables were summarized using the Safety Set (SS), which consisted of all randomized subjects who had received at least 1 dose of study medication.

For AE tables, in addition to the placebo group, placebo subjects escaping to CZP 200mg Q2W or 400mg Q4W were displayed separately utilizing their CZP data depending on the dose at onset of the AE. Also, in addition to the 2 CZP groups (200mg Q2W, 400mg Q4W), an “All CZP” group was used (200mg Q2W, 400mg Q4W, and the escaped placebo subjects with their CZP data).

The following 3 safety sets were used for the pooled analyses in the AS001 clinical cut (data cutoff 31 May 2012):

- The Double-Blind Safety Pool (Pool S1) consisted of subjects who received at least 1 dose of CZP in the completed Double-Blind Treatment Period of AS001. Data for the placebo-escape subjects were included in the CZP 200mg Q2W or CZP 400mg Q4W groups. This is in contrast to the AS001 Week 24 CSR, where the CZP data for placebo-escape subjects were presented separately and not included in the individual CZP groups but rather in the All CZP group.
- The All CZP Safety Pool (Pool S2) consisted of subjects who received at least 1 dose of CZP in AS001. Data up to the last completed visit before or on 31 May 2012 were utilized and includes data from the Double-Blind, Dose-Blind, and Open-Label Treatment Periods.
- The SS consisted of all randomized subjects who received at least 1 dose of study medication (CZP or placebo), which is the same definition used in the AS001 Week 24 SAP for the AS001 Week 24 CSR. This analysis set was used to rerun select tables and listings for updates obtained

after the database lock for the Week 24 Double-Blind Treatment Period (i.e., AEs that were not included in the CSR) and for updates for the placebo-escape subjects.

Patient exposure

A total of 298 subjects have been exposed to at least 1 dose of CZP in the ongoing Dose-Blind Treatment Period and 257 of these subjects have completed the Dose-Blind Treatment Period (total study duration of 48 weeks) and have entered the Open-Label Treatment Period; 260 subjects are currently ongoing in either the Dose-Blind or Open-Label Treatment Periods of the study. Overall, a total of 205 subjects have been exposed to CZP for at least 12 months.

In the AS001 Week 24 data, the exposure was 108.8 pt-yrs for subjects while on CZP and 38.9 pt-yrs for subjects while on placebo.

As of the data cutoff date (31 May 2012), 65.1% of subjects had been treated with CZP for at least 12 months, which equaled 278 pt-yrs of exposure. A total of 23.2% of subjects had received CZP for ≥6 to <12 months, 44.1% had received CZP for ≥12 to <18 months, and 20.3% had received CZP for ≥18 to <24 months.

Table 11 Extent of exposure: AS001 (data cutoff 31 May 2012) All CZP Safety Pool (SS As Treated)

	Double-Blind Safety Pool (S1)			All CZP Safety Pool (S2)		
	CZP 200mg Q2W N=138	CZP 400mg Q4W N=136	All CZP N=274	CZP 200mg Q2W N=158	CZP 400mg Q4W N=157	All CZP N=315
Patient-years of exposure	54.8	52.9	107.7	181.4	177.7	359.1
Duration of exposure in narrow sense (days)[a]						
Mean (SD)	139.0 (45.8)	137.5 (48.8)	138.3 (47.2)	403.9 (153.3)	399.9 (156.6)	401.9 (154.8)
Median	167.0	168.0	167.0	408.5	419.0	410.0
Min, max	41, 173	14, 172	14, 173	41, 730	14, 755	14, 755
Duration of exposure in broader sense (days)[b]						
Mean (SD)	145.2 (44.9)	142.0 (48.5)	143.6 (46.7)	419.4 (145.6)	413.3 (151.2)	416.3 (148.2)
Median	168.0	168.0	168.0	420.0	420.0	420.0
Min, max	54, 182	14, 214	14, 214	56, 730	14, 755	14, 755

CZP=certolizumab pegol; min=minimum; max=maximum; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation; SS=Safety Set
Note: The CZP 200mg Q2W and CZP 400mg Q4W groups in the Double-Blind Safety Pool include subjects escaping from PBO to CZP at Week 16, utilizing their CZP data only. The CZP 200mg Q2W and CZP 400mg Q4W groups in the All CZP Safety Pool include, in addition, subjects switching from PBO to CZP at Week 24, utilizing their CZP data only.
[a] Exposure in narrow sense=last injection date - first injection date+14 (or +28) days.
[b] Exposure in broader sense=last injection date - first injection date+70 days.

Because it consists of a single Phase 3 study, the axSpA program is supported by safety data from the large RA program and comparisons are made between the safety data for axSpA and RA. Supportive data on the safety of CZP are provided from a pooling of 14 RA studies (12 completed studies and 2 ongoing studies with a cutoff date of 30 Nov 2011) that includes 4049 subjects and 9277 patient-years (pt-yrs).

Adverse events

Common adverse events

In the AS001 Week 24 CSR data, the incidence of treatment emergent adverse events (TEAEs) was 70.4% in the All CZP group and 62.6% in the placebo group; the incidence was similar between the CZP 200mg Q2W and CZP 400mg Q4W groups (76.6% and 74.8%, respectively; Table 12). Severe TEAEs were reported in 3.6% of subjects in the All CZP group and 6.5% in the placebo group. The incidence of drug related TEAEs was higher in the All CZP group (33.2%) compared with placebo (20.6%).

Table 12 Overall summary of TEAEs during the 24-week Double-Blind Treatment Period (SS)

	PBO N=107 n (%)	CZP 200mg Q2W N=111 n (%)	CZP 400mg Q4W N=107 n (%)	All CZP N=274 n (%)
Any TEAEs	67 (62.6)	85 (76.6)	80 (74.8)	193 (70.4)
TEAEs by intensity:				
Mild	52 (48.6)	65 (58.6)	64 (59.8)	154 (56.2)
Moderate	36 (33.6)	46 (41.4)	43 (40.2)	99 (36.1)
Severe	7 (6.5)	4 (3.6)	3 (2.8)	10 (3.6)
Drug-related[a] TEAEs	22 (20.6)	41 (36.9)	36 (33.6)	91 (33.2)
Serious TEAEs	5 (4.7)	4 (3.6)	7 (6.5)	13 (4.7)
Discontinuation due to TEAEs	2 (1.9)	2 (1.8)	4 (3.7)	6 (2.2)
Death	0	0	0	0

CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: For the entire placebo group, CZP data from placebo subjects were not utilized.
Note: The All CZP group includes CZP 200mg Q2W, CZP 400mg Q4W, and the escaped placebo subjects with their CZP data.
[a] Drug-related TEAEs are those with a relationship of related, possibly related, or those with a missing response.

In the All CZP Safety Pool, the incidence of TEAEs overall was 81.9% in the All CZP group; the incidence was higher in the CZP 200mg Q2W group compared with the CZP 400mg Q4W group (87.3% vs 76.4%; Table 5-3). The incidences of drug-related TEAEs, severe TEAEs, SAEs, and discontinuations due to TEAEs were similar between the CZP 200mg Q2W and CZP 400mg Q4W groups.

Table 13 Overall summary of TEAEs: AS001 (data cutoff 31 May 2012) (SS As Treated)

	Double-Blind Safety Pool (S1)			All CZP Safety Pool (S2)		
	CZP 200mg Q2W N=138 n (%)	CZP 400mg Q4W N=136 n (%)	All CZP N=274 n (%)	CZP 200mg Q2W N=158 n (%)	CZP 400mg Q4W N=157 n (%)	All CZP N=315 n (%)
Any TEAEs	101 (73.2)	92 (67.6)	193 (70.4)	138 (87.3)	120 (76.4)	258 (81.9)
Severe TEAEs	7 (5.1)	3 (2.2)	10 (3.6)	15 (9.5)	11 (7.0)	26 (8.3)
Drug-related[a]TEAEs	47 (34.1)	42 (30.9)	89 (32.5)	67 (42.4)	66 (42.0)	133 (42.2)
Serious TEAEs	6 (4.3)	8 (5.9)	14 (5.1)	17 (10.8)	13 (8.3)	30 (9.5)
Discontinuation due to TEAEs	2 (1.4)	4 (2.9)	6 (2.2)	12 (7.6)	13 (8.3)	25 (7.9)
Death	0	0	0	0	0	0

CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: The CZP 200mg Q2W and CZP 400mg Q4W groups in the Double-Blind Safety Pool include subjects escaping from PBO to CZP at Week 16, utilizing their CZP data only. The CZP 200mg Q2W and CZP 400mg Q4W groups in the All CZP Safety Pool include in addition subjects switching from PBO to CZP at Week 24, utilizing their CZP data only.
[a] Drug-related TEAEs are those with a relationship of related, possibly related, or those with a missing response.

In the AS001 Week 24 CSR data, TEAEs in the All CZP group were most commonly reported in the SOC of Infections and infestations (34.7% vs 23.4% in the placebo group), followed by the SOCs of Skin and subcutaneous tissue disorders (14.6% vs 13.1% in the placebo group), Gastrointestinal disorders (13.9% vs 14.0% in the placebo group), Investigations (13.5% vs 6.5% in the placebo group), and General disorders and administration site conditions (12.4% vs 7.5% in the placebo group). Of note, the placebo group reported a higher incidence of TEAEs in the SOC of Musculoskeletal and connective tissue disorders compared with the All CZP group (19.6% vs 8.0%).

The most commonly reported TEAEs (by PT) in the All CZP group were nasopharyngitis (8.8% vs 6.5% for placebo), headache (6.2% vs 6.5%, respectively), and blood creatine phosphokinase increased (5.1% vs 1.9%, respectively); only blood creatine phosphokinase increased occurred in a higher percentage of subjects in the All CZP group compared with the placebo group (difference of ≥3%). Elevated CK AEs were not associated with increased cardiac or musculoskeletal AEs based on a manual review of AEs (including reported terms) and concomitant medications in all subjects with markedly abnormal CK values.

Incidences of the most commonly reported TEAEs (by PT) were generally similar between the CZP 200mg Q2W and CZP 400mg Q4W groups, with the exception of (difference of ≥3%) pharyngitis (4.5% vs 0.9%, respectively).

Table 14 Summary of TEAEs in all SOCs, including PTs with an incidence of at least 2% in all CZP subjects: Double-Blind Treatment Period (SS As Randomized)

System Organ Class Preferred term	PBO N=107 n (%)	CZP 200mg Q2W N=111 n (%)	CZP 400mg Q4W N=107 n (%)	All CZP N=274 n (%)
Any TEAE	**67 (62.6)**	**85 (76.6)**	**80 (74.8)**	**193 (70.4)**
Blood and lymphatic system disorders	5 (4.7)	5 (4.5)	5 (4.7)	11 (4.0)
Cardiac disorders	1 (0.9)	2 (1.8)	2 (1.9)	5 (1.8)
Congenital, familial, and genetic disorders	1 (0.9)	0	0	0
Ear and labyrinth disorders	1 (0.9)	1 (0.9)	2 (1.9)	3 (1.1)
Eye disorders	5 (4.7)	6 (5.4)	5 (4.7)	13 (4.7)
Gastrointestinal disorders	15 (14.0)	15 (13.5)	15 (14.0)	38 (13.9)
Nausea	1 (0.9)	4 (3.6)	2 (1.9)	7 (2.6)
General disorders and administration site conditions	8 (7.5)	17 (15.3)	11 (10.3)	34 (12.4)
Fatigue	1 (0.9)	3 (2.7)	3 (2.8)	6 (2.2)
Injection site erythema	0	3 (2.7)	3 (2.8)	7 (2.6)
Hepatobiliary disorders	1 (0.9)	0	3 (2.8)	3 (1.1)
Immune system disorders	2 (1.9)	2 (1.8)	4 (3.7)	6 (2.2)
Infections and infestations	25 (23.4)	43 (38.7)	41 (38.3)	95 (34.7)
Folliculitis	0	3 (2.7)	2 (1.9)	6 (2.2)
Bronchitis	1 (0.9)	4 (3.6)	1 (0.9)	6 (2.2)
Nasopharyngitis	7 (6.5)	11 (9.9)	11 (10.3)	24 (8.8)
Upper respiratory tract infection	3 (2.8)	6 (5.4)	4 (3.7)	11 (4.0)
Pharyngitis	1 (0.9)	5 (4.5)	1 (0.9)	7 (2.6)
Urinary tract infection	4 (3.7)	2 (1.8)	3 (2.8)	7 (2.6)
Injury, poisoning, and procedural complications	7 (6.5)	10 (9.0)	6 (5.6)	16 (5.8)
Investigations	7 (6.5)	19 (17.1)	16 (15.0)	37 (13.5)
Blood creatine phosphokinase increased	2 (1.9)	7 (6.3)	6 (5.6)	14 (5.1)
Metabolism and nutrition disorders	3 (2.8)	6 (5.4)	5 (4.7)	12 (4.4)
Musculoskeletal and connective tissue disorders	21 (19.6)	12 (10.8)	7 (6.5)	22 (8.0)
Neoplasms benign, malignant, and unspecified (including. cysts and polyps)	0	0	1 (0.9)	1 (0.4)
Nervous system disorders	12 (11.2)	12 (10.8)	14 (13.1)	28 (10.2)
Headache	7 (6.5)	7 (6.3)	9 (8.4)	17 (6.2)
Psychiatric disorders	5 (4.7)	4 (3.6)	7 (6.5)	11 (4.0)
Renal and urinary disorders	2 (1.9)	0	6 (5.6)	7 (2.6)
Reproductive system and breast disorders	1 (0.9)	1 (0.9)	4 (3.7)	5 (1.8)
Respiratory, thoracic and mediastinal disorders	6 (5.6)	14 (12.6)	5 (4.7)	19 (6.9)
Cough	1 (0.9)	5 (4.5)	2 (1.9)	7 (2.6)
Skin and subcutaneous disorders	14 (13.1)	17 (15.3)	16 (15.0)	40 (14.6)
Rash	2 (1.9)	3 (2.7)	4 (3.7)	12 (4.4)
Vascular disorders	6 (5.6)	4 (3.6)	5 (4.7)	14 (5.1)
Hypertension	4 (3.7)	3 (2.7)	2 (1.9)	8 (2.9)

CZP=certolizumab pegol; PBO=placebo; PT=preferred term; Q2W=every 2 weeks; Q4W=every 4 weeks; SOC=System Organ Class; SS=Safety Set; TEAE=treatment-emergent adverse event

Note: For the entire placebo group, CZP data from placebo subjects were not utilized.

Note: The All CZP group includes CZP 200mg Q2W, CZP 400mg Q4W, and the escaped placebo subjects with their CZP data.

The incidence of TEAEs overall was higher in the CZP 200mg Q2W group compared with the CZP 400mg Q4W group in both the Double-Blind Safety Pool (73.2% vs 67.6%, respectively) and the All CZP Safety Pool (87.3% vs 76.4%, respectively); the corresponding incidence rates were also higher (Double-Blind Safety Pool: 388 vs 350 per 100 pt-yrs, respectively; All CZP Safety Pool: 270 vs 181 per 100 pt-yrs, respectively). Although some differences in individual System Organ Classes (SOCs) and/or higher level terms (HLTs) were observed that could have contributed to this difference between the dose regimens, no clearly discernible reason for this difference was apparent, and no confounding demographic or baseline disease characteristics were identified that could have contributed to this difference. This difference between the dose regimens was not seen in the RA studies.

The MAH argued that in the CZP RA studies, the AE profile of CZP was as expected for an anti-TNFα therapy and was consistent with previous experience with CZP across indications. No new safety alerts were identified. There were more TEAEs in the CZP groups compared with the placebo group, and there was a comparable percentage of severe TEAEs across the CZP groups and placebo. There was generally no increase in incidence rates with long-term exposure. The AE profiles in the AS001 study and the CZP RA studies were generally similar; however, in the axSpA population, an increase in CK was among the most common TEAEs, which was not seen in the RA studies.

Significant adverse events

Infections

The incidence of infection TEAEs was higher in CZP-treated vs placebo-treated subjects (34.7% vs 23.4%, respectively) during the 24-week Double-Blind Treatment Period. There was no increased risk of infections or serious infections overall with longer exposure to CZP.

Other than the SAE of oesophageal candidiasis, no other rare or opportunistic infections or cases of tuberculosis (TB) were reported during the 24-week Double-Blind Treatment Period. Per protocol, and in accordance with 2012 American College of Rheumatology recommendations, as an additional safety measure, subjects with negative purified protein derivative (PPD) tests at entry were retested for TB at Weeks 48 and 96. Subjects with PPD conversion were to be withdrawn from the study unless the absence of latent or active TB was confirmed by additional assessments. Overall, 14 subjects had either a positive PPD test or suspected latent or active TB recorded as a TEAE at the time of the data cutoff (31 May 2012). One subject was confirmed to have active TB, while active or latent TB was excluded by additional monitoring in 4 subjects (in the remaining 9 subjects, latent or active TB was neither confirmed nor excluded).

In the RA studies, there was an increase in the overall incidence of infections, serious infections, and infections leading to withdrawal with CZP therapy compared with placebo; however, there was no increase in risk with increased duration of exposure.

The profile of infections associated with CZP treatment was generally similar between the AS001 population and the RA studies and is consistent with other anti-TNFα therapies.

Malignancy

A single potential malignancy was reported with CZP treatment during AS001 (lung neoplasm [reported term: nodule on left lower lobe on chest x-ray], which was mild, nonserious, and did not lead to discontinuation from study drug). There was no evidence of an increased risk of malignancies with longer exposure to CZP.

In the RA studies, the overall incidence of malignancies was similar between CZP-treated and placebo-treated subjects. There was no evidence of an increased risk of malignancies with longer exposure to CZP.

Autoimmune disorders

In AS001, there were no reports of autoimmune disorders such as lupus-like illness, development of autoantibodies, or sarcoidosis. Three cases of pustular psoriasis were reported with CZP treatment during the study.

Cardiovascular

During the Double-Blind Treatment Period, the incidence of TEAEs in the Cardiac disorders SOC was low in the All CZP (1.8%) and placebo (0.9%) groups. Hypertension was the most commonly reported vascular event in all groups, with no difference in incidence between the All CZP and placebo groups (2.9% and 3.7%, respectively). All other vascular events (by PT) were reported in 2 or fewer subjects. The profile of cardiovascular (CV) and vascular events did not change and there was no increased risk of CV or vascular events with longer exposure to CZP.

The profile of CV events associated with CZP treatment was generally similar between the AS001 population and the RA studies and is consistent with other anti-TNFα therapies

Neurological events

There have been no TEAEs suggestive of demyelinating disorders reported during AS001 through the cutoff date of 31 May 2012.

Hematology

Reports of leukopenia, neutropenia, and thrombocytopenia were rare throughout AS001; all of these events were nonserious and mild or moderate in intensity and there was no increased risk with longer exposure to CZP.

Serious bleeding events

There were no SAEs of bleeding events reported during the 24-week Double-Blind Treatment Period of AS001 (including the reanalysis data) or during the clinical cut

Hepatic system

During the Double-Blind Treatment Period, the incidence of TEAEs related to liver function parameters was similar in the All CZP group compared with the placebo group. The most commonly reported hepatic TEAEs throughout the study were alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, and gamma glutamyltransferase (GGT) increased. Concomitant use of disease modifying antirheumatic drug (DMARDs; eg, methotrexate [MTX]) resulted in a higher incidence of hepatic TEAEs with CZP treatment compared with placebo (9.8% in the All CZP group vs 5.3% in the placebo group),

There was no increased risk in hepatic TEAEs (overall or by Baseline use of DMARDs) with long-term CZP exposure. A very high elevation in ALT (≥10xULN) was reported in 1 subject in the CZP 200mg Q2W group.

In both the axSpA and RA populations, the most common hepatic events were in liver function analyses, particularly ALT increased. In subjects with axSpA, CZP treatment resulted in elevated ALT values in a small percentage of subjects, which is consistent with other anti-TNFα medications (eg, infliximab and adalimumab).

Serious skin disorders

There were no SAEs of skin reactions reported during the 24-week Double-Blind Treatment Period of AS001 (including the reanalysis data) or in the clinical cut.

Injection reactions (including hypersensitivity)

In the Double-Blind Treatment Period, injection site erythema was the most common injection reaction, with an incidence of 2.6% in the All CZP group compared with 0 in the placebo group. The incidence of acute and delayed systemic hypersensitivity injection reactions was low (≤1.9% in both the All CZP and placebo groups). There was no increased TEAE risk of any type of injection/hypersensitivity reaction with longer exposure to CZP.

In the RA studies, as expected, more injection site reactions and hypersensitivity events occurred in subjects treated with CZP compared with placebo; however, the incidence of these events did not increase with increased exposure to CZP

The profile of injection and hypersensitivity reactions associated with CZP treatment was generally similar between the AS001 population and the RA studies.

Other events

Two events of alopecia, 1 SAE of retinal vein occlusion, and 1 TEAE of eosinophilic bronchitis were reported. There were no pregnancies reported during the Double-Blind Treatment Period of AS001. A total of 3 pregnancies were reported during the clinical cut period

Immunogenicity

In AS001, there were too few antibody-positive subjects to draw meaningful conclusions regarding AEs by anti-CZP antibody status.

Serious adverse event / deaths / other significant events

Serious AEs were reported in 4.7% of subjects in both the placebo and All CZP groups, although the incidence was slightly higher in the CZP 400mg Q4W group compared with CZP 200mg Q2W (6.5% vs 3.6%). The incidence of TEAEs leading to discontinuation was similar in the All CZP and placebo groups (2.2% and 1.9%, respectively).

No deaths were reported during the Double-Blind Treatment Period of AS001.

Laboratory findings

In the axSpA population, an increase in CK was among the most common TEAEs, which was not seen in the RA studies.

In the AS001 Week 24 the TEAE blood creatine phosphokinase increased was reported in a higher percentage of subjects in the All CZP group compared with the placebo group (5.1% vs 1.9%).

In the clinical cut data, the AE blood creatine phosphokinase increased was reported by 6.7% of subjects in the All CZP Safety Pool and 4.4% in the Double-Blind Safety Pool; however, the incidence rate was lower in the All CZP Safety Pool compared with the Double-Blind Safety Pool (6.19 vs 11.52 per 100 pt-yrs), suggesting that there is no increased risk of elevation in CK with long-term exposure to CZP. Five subjects (1.6%) in the All CZP Safety Pool and 1 subject (0.4%) in the Double-Blind Safety Pool reported elevations in CK that were considered severe. These findings were not associated with cardiac symptoms or events. Of note, the incidence of blood creatine phosphokinase increased TEAEs was higher in males compared with females in the All CZP Safety Pool (9.2% vs. 2.5% in the All CZP groups) and in the Double-Blind Safety Pool (5.3% vs 2.9% in the All CZP groups).

Safety in special populations

Adverse events by concomitant medication use

As some DMARDs are known to be potentially hepatotoxic, a focused search on hepatic events by Baseline use of DMARDs was performed using the reanalysis data for the 24-week Double-Blind Treatment Period and the clinical cut data for AS001.

In the reanalysis data for the 24-week Double-Blind Treatment Period, in subjects with Baseline DMARD use, the incidence of hepatic TEAEs was higher in the All CZP group compared with the placebo group (9.8% vs 5.3%); this difference in the incidence of hepatic AEs between the All CZP and placebo groups was not observed in subjects not using DMARDs at Baseline (4.7% vs 4.3%, respectively).

In the clinical cut data, the types of hepatic TEAEs were similar in the All CZP Safety Pool and the Double-Blind Safety Pool regardless of Baseline DMARD use. In the All CZP group, the incidence of hepatic TEAEs was higher in subjects with Baseline DMARD use compared with subjects without Baseline DMARD use in both the All CZP Safety Pool (14.4% vs 7.8%, respectively) and the Double-Blind Safety Pool (8.5% vs 3.6%, respectively). The difference in incidence of hepatic events between the subgroups is largely due to differences within the CZP 200mg Q2W group, in which hepatic TEAEs were reported by 12.8% of subjects with Baseline DMARD use compared with 4.0% of subjects without Baseline DMARD use. However, given the small number of subjects reporting hepatic events in each subgroup (n's=8 and 6), it is difficult to make meaningful conclusions regarding differences between these subgroups.

The incidence rate of hepatic TEAEs overall did not increase with long-term exposure to CZP, nor did the incidence rates of most hepatic events (by PT), including the most common (ALT increased, AST increased, and GGT increased).

Adverse events by gender

Using the clinical cut data, TEAEs were analyzed by gender.

Table 15 Overall summary of TEAEs in the All CZP Safety Pool by gender: AS001 (data cutoff 31 May 2012) (SS As Treated)

	Males			Females		
	All CZP Safety Pool (S2)			All CZP Safety Pool (S2)		
	CZP 200mg Q2W N=92 n (%)	CZP 400mg Q4W N=104 n (%)	All CZP N=196 n (%)	CZP 200mg Q2W N=66 n (%)	CZP 400mg Q4W N=53 n (%)	All CZP N=119 n (%)
Any TEAEs	76 (82.6)	76 (73.1)	152 (77.6)	62 (93.9)	44 (83.0)	106 (89.1)
Severe TEAEs	7 (7.6)	9 (8.7)	16 (8.2)	8 (12.1)	2 (3.8)	10 (8.4)
Drug-related[a] TEAEs	34 (37.0)	42 (40.4)	76 (38.8)	33 (50.0)	24 (45.3)	57 (47.9)
Serious TEAEs	11 (12.0)	7 (6.7)	18 (9.2)	6 (9.1)	6 (11.3)	12 (10.1)
Discontinuation due to TEAEs	8 (8.7)	8 (7.7)	16 (8.2)	4 (6.1)	5 (9.4)	9 (7.6)
Death	0	0	0	0	0	0

CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SS=Safety Set; TEAE=treatment-emergent adverse event

Note: The CZP 200mg Q2W and CZP 400mg Q4W groups in the Double-Blind Safety Pool include subjects escaping from PBO to CZP at Week 16, utilizing their CZP data only. The CZP 200mg Q2W and CZP 400mg Q4W groups in the All CZP Safety Pool include in addition subjects switching from PBO to CZP at Week 24, utilizing their CZP data only.

Note: Denominators are based on N, the number of subjects in the given treatment group for the subgroup indicated.

[a] Drug-related TEAEs are those with a relationship of related, possibly related, or those with missing responses.

Adverse events in the AS and nr-axSpA subpopulations

Using the clinical cut data, TEAEs were analyzed separately for subjects in the AS and nr-axSpA subpopulations. In the All CZP group in the All CZP Safety Pool, there was no meaningful difference between subjects with AS or nr-axSpA with regard to the reporting of TEAEs overall, severe TEAEs, or serious TEAEs. Subjects in the AS subpopulation reported a higher incidence of TEAEs leading to discontinuation (9.8%) compared with subjects in the nr-axSpA subpopulation (5.7%), and a lower incidence of drug-related TEAEs (36.8% vs 48.9%, respectively).

Safety in RA and CD populations

A comprehensive summary of RA safety data that includes 4049 subjects and 9277 patient-years was provided. Overall, the incidence and pattern of AEs observed in the CZP RA clinical development program are consistent with those expected for RA subjects on anti-TNFα therapy. In general, long-term exposure to CZP (>60 months) was not associated with an increased safety signal.

A brief summary of the CZP safety profile in 2518 CD subjects with an estimated total of 2837.0 patient-years exposure to CZP treatment was provided. Overall, the AE profile for CZP described in subjects with CD is typical of an anti-TNFα agent. None of the data suggest any new safety signals following longer-term treatment with CZP in subjects with CD.

Safety related to drug-drug interactions and other interactions

No specific analyses included.

Discontinuation due to adverse events

In the AS001Week 24 CSR, the overall incidence of TEAEs leading to permanent study medication discontinuation was similar between the All CZP group (2.2%) and the placebo group (1.9%), as well as between the CZP 200mg Q2W (1.8%) and CZP 400mg Q4W groups (3.7%). The most common TEAEs that led to withdrawal in the All CZP group were in the SOCs of Infections and infestations (2 subjects, 0.7%). No individual TEAE leading to permanent study medication discontinuation was reported by more than 1 subject.

Table 16 TEAEs leading to permanent study medication discontinuation: Double-Blind Treatment Period (SS)

System Organ Class Preferred term	PBO N=107 n (%)	CZP 200mg Q2W N=111 n (%)	CZP 400mg Q4W N=107 n (%)	All CZP N=274 n (%)
Any TEAEs leading to permanent study medication discontinuation	2 (1.9)	2 (1.8)	4 (3.7)	6 (2.2)
General disorders and administration site conditions	1 (0.9)	0	0	0
Non-cardiac chest pain	1 (0.9)	0	0	0
Hepatobiliary disorders	1 (0.9)	0	1 (0.9)	1 (0.4)
Cholelithiasis	0	0	1 (0.9)	1 (0.4)
Hepatitis	1 (0.9)	0	0	0
Immune system disorders	0	0	1 (0.9)	1 (0.4)
Hypersensitivity	0	0	1 (0.9)	1 (0.4)
Infections and infestations	0	2 (1.8)	0	2 (0.7)
Folliculitis	0	1 (0.9)	0	1 (0.4)
Upper respiratory tract infection	0	1 (0.9)	0	1 (0.4)
Investigations	0	0	1 (0.9)	1 (0.4)
C-reactive protein increased[a]	0	0	1 (0.9)	1 (0.4)
Reproductive system and breast disorders	0	0	1 (0.9)	1 (0.4)
Gynaecomastia	0	0	1 (0.9)	1 (0.4)

CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: For the entire placebo group, CZP data from placebo subjects were not utilized.
Note: The All CZP group includes CZP 200mg Q2W, CZP 400mg Q4W, and the escaped placebo subjects with their CZP data.
[a] This event was reported at the subject's Early Termination Visit.

As expected, a higher percentage of subjects in the All CZP group in the All CZP Safety Pool (7.9%) reported TEAEs leading to withdrawal compared with the Double-Blind Safety Pool (2.2%). The most common TEAEs that led to withdrawal in the All CZP Safety Pool were in the SOCs of Infections and infestations (3.5%), Investigations (1.3%), and Skin and subcutaneous tissue disorders (1.0%).

The incidence rate of TEAEs leading to withdrawal was slightly higher with long-term exposure (7.05 per 100 pt-yrs in the All CZP Safety Pool vs 5.62 per 100 pt-yrs in the Double-Blind Safety Pool). This was primarily attributed to an increase in the incidence rate of TEAEs in the SOC Infections and infestations (3.08 per 100 pt-yrs in the All CZP Safety Pool vs 1.86 per 100 pt-yrsin the Double-Blind Safety Pool). This was due, in part, to an increase in the HLTs tuberculous infections and mycobacteria identification and serology, which are discussed earlier in this document. The only other TEAE leading to withdrawal (by HLT) that had a higher incidence rate with long-term exposure was psoriatic conditions, which occurred at a rate of 0.56 vs 0 per 100 pt-yrs (2 subjects vs 0 subjects); however, the incidence rate was very low in the All CZP Safety Pool.

An imbalance in the incidence rate of TEAEs leading to withdrawal overall between the CZP 200mg Q2W and CZP 400mg Q4W groups was observed in the Double-Blind Safety Pool (3.67 vs 7.65 per 100 pt-yrs, respectively); however, this difference was diminished with longer CZP exposure (6.69 vs 7.41 per 100 pt-yrs).

Post-marketing experience

The MAH concluded that adverse reactions reported from global post-marketing experience for the approved indications of RA and CD (not approved in the EU) were reviewed, and no safety related findings that may have an impact on benefit/risk ratio of CZP in relation to the new indication for axSpA have been identified.

Safety in RA subjects

A full analysis of safety in RA subjects is provided in the Integrated Summary of RA Safety Data. Pooled data are presented from 14 studies in adult subjects with RA, which includes 12 completed studies and 2 ongoing open-label extension studies (C87028 and C87051), with the clinical cutoff date of 30 Nov 2011.

The pooled database for the RA Population includes 4049 subjects treated with any CZP dose (primarily 200mg Q2W, 400mg Q2W, or 400mg Q4W given sc) in placebo-controlled or open-label studies with an estimated total of 9277 pt-yrs exposure to CZP treatment (calculated as last dose date–first dose date+1 dosing interval [14 or 28 days]). The database includes 1137 subjects who received placebo.

Overall, the incidence and pattern of AEs observed in the CZP clinical development program are consistent with those expected for RA subjects on anti-TNFα therapy.

2.5.2. Discussion on clinical safety

The adverse event profile of CZP was as expected for an anti-TNFα therapy and was consistent with previous experience with CZP. The most commonly reported TEAEs in the All CZP group were nasopharyngitis (8.8% vs 6.5% for placebo), headache (6.2% vs 6.5%, respectively), and blood creatine phosphokinase increased (5.1% vs 1.9%, respectively); of those, only the AE "blood creatine phosphokinase increased" occurred in a higher percentage of subjects in the All CZP group compared with the placebo group (difference of ≥3%). This increase in CPK, among the most common TEAEs, was not commonly seen in the RA studies. There did not seem to be an increased risk of elevation in CPK with long-term exposure to CZP. These findings were not associated with cardiac symptoms or events. The incidence of blood creatine phosphokinase increased TEAEs was higher in males compared with females. The frequency was increased both in patients treated with placebo (2.8% vs 0.4% in axSpA and RA populations, respectively) as well as in patients treated with Cimzia (4.7% vs 0.8% in axSpA and RA populations, respectively). The CPK elevations in the axSpA study were mostly mild to moderate, transient in nature and of unknown clinical significance with no cases leading to withdrawal.

Creatine phosphokinase is currently listed as "uncommon" in the SmPC. In AS 001 it appeared to have been very common. During the procedure, the MAH was requested to provide a tabulated review of all cases with values, reference values, time to onset, concomitant medications, outcome and associated AEs. The reanalysis was provided, and upon review it was confirmed that the overall frequency of creatine phosphokinase in Cimzia studies remain "uncommon". However, the CHMP considered justified adding in section 4.8 in the SmPC that the frequency of CPK elevations was generally higher in patients with axSpA as compared to the RA population. This was accepted by the MAH.

In AS001 study, there were 3 cases of pustular psoriasis among the CZP-treated subjects, which may indicate a risk for provoking pustular psoriasis in patients prone to the disease. The MAH should therefore report all cases of pustular psoriasis per indication in the future PSURs.

No death was reported in the pivotal study AS001. The most common serious AEs (SAEs) in the Double-Blind Treatment Period were infections (1.1% vs 0 for placebo). For all other SOCs, the incidence was ≤0.7%. No individual SAE (by PT) was reported by more than 1 subject. In the All CZP Safety Pool, SAEs were reported most often in the SOC of Infections and infestations (3.5% for the All CZP group).

No differences between dosing regimens CZP 200mg Q2W and CZP 400mg Q4W were seen in incidence of drug-related TEAEs, severe TEAEs, SAEs, or discontinuations due to TEAEs. The incidence and incidence rate of TEAEs overall were higher in the CZP 200mg Q2W group compared with the CZP 400mg Q4W group (91.8% vs 82.8% and 246.73 vs 162.70 per 100 pt-yrs, respectively). During the

procedure the MAH showed that this was consistent with the original filing for the RA indication and that the incidence rates in both groups were lower than in the original filing (269.85 and 180.50 per 100 pt-yrs, respectively), indicating no increased risk of TEAEs with longer exposure with either dosing regimen. The SOCs contributing to the differences between the dosing regimens were not typically those of concern for anti-TNFα agents and no differences between dosing regimens were seen for SOCs typically of concern with anti-TNFα agents (i.e. infections). Overall, the CHMP considered that there was no clinical meaningful difference between the 2 treatment regimens with respect to safety.

In the All CZP group in the All CZP Safety Pool, there was no meaningful difference between subjects with AS or nr-axSpA with regard to the reporting of TEAEs overall, severe TEAEs, or serious TEAEs. Subjects in the AS subpopulation reported a higher incidence of TEAEs leading to discontinuation (9.8%) compared with subjects in the nr-axSpA subpopulation (5.7%), and a lower incidence of drug-related TEAEs (36.8% vs 48.9%, respectively). Comparisons of adverse events between the AS and nr-axSpA subpopulations would not permit any firm conclusions, as the groups appeared to be mixed in regard to AS and nraAxSpA due to the use of historical x-ray data. Upon request the MAH presented a reanalysis of TEAEs in AS and nraAxSpA patients, with classification based on the x-ray data from baseline. The data showed that the initial safety conclusions in the respective groups are not impacted.

2.5.3. Conclusions on clinical safety

CZP was generally well tolerated during in study AS001. The most common AE was non serious infections, such as nasopharyngitis. No new safety signal has been identified in the AxSpA population studied in AS001. Comparisons were made to the RA safety databases. The safety profile for axSpA patients was consistent with the safety profile in RA and previous experience with Cimzia, with the exception of CPK elevations which were generally higher in patients with axSpA as compared to the RA population. The CPK elevations in the axSpA study were mostly mild to moderate, transient in nature and of unknown clinical significance with no cases leading to withdrawal. This information was reported in the SmPC and CPK elevations remain listed as an uncommon event in the SmPC. In AS001 study, there were 3 cases of pustular psoriasis in the CZP-treated patients, which may indicate a risk for provoking pustular psoriasis in patients prone to the disease. Pustular psoriasis is already listed as an uncommon event in the SmPC. The MAH will closely follow-up and report all cases of pustular psoriasis per indication in the future PSURs.

As described in the RMP the MAH will submit the final results of Study AS001 by Q2 2016 which will bring additional data to further characterize the long term safety profile of CZP treatment in axial spondyloarthritis patients up to 204 weeks of treatment. Safety data after treatment withdrawal and re-introduction will also become available from the planned blinded withdrawal trial (see discussion on efficacy) or which results are expected in January 2019 as detailed in the RMP.

The CHMP considers the following measures necessary to address issues related to safety:

- Study AS001: Phase 3, multicenter, randomized, double blind, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in subjects with active axial spondyloarthritis (axial SpA)

- Remission/withdrawal study in early axial spondyloarthritis

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 9.2, the PRAC considers by consensus that the risk management system for certolizumab pegol in the treatment:

- of moderate to severe, active rheumatoid arthritis (RA) in adult patients in combination with methotrexate when the response to disease-modifying antirheumatic drugs (DMARDs) including methotrexate, has been inadequate.
  Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.
  Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

- of adult patients with severe active axial spondyloarthritis, comprising:
  - Ankylosing spondylitis (AS)

  Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).
  - Axial spondyloarthritis without radiographic evidence of AS

  Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to NSAIDs.

is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Table 17 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Infections including TB and serious opportunistic infections • Moderate to severe congestive heart failure (NYHA class III/IV) • Hypersensitivity reactions • Malignancies including lymphoma, leukemia, Merkel cell carcinoma, Hepatosplenic T-cell lymphoma, and melanoma • Demyelinating-like disorders • Aplastic anemia, neutropenia, thrombocytopenia, pancytopenia, and leukopenia • Lupus and lupus-like illness • Immunogenicity including sarcoidosis • New onset or worsening of psoriasis (including palmoplantar pustular psoriasis) and related conditions • Hepatobiliary events including hepatitis, hepatic enzymes increased, and cholestasis
Important potential risks	• Ischemic cardiac events • Serious bleeding events • Hepatitis B virus reactivation

Important missing information	• Pregnancy and lactation • Children and adolescents • Elderly • Patients with renal or hepatic impairment • Potential for overdose • Potential for medication errors • Off-label use • Concomitant use with DMARDs other than MTX • Use by patients with prior anti-TNF use • Vaccination • Long-term use in axial spondyloarthritis

DMARD=disease modifying antirheumatic drug, MTX=methotrexate, NYHA=New York Heart Association, TB=tuberculosis, TNFα=tumor necrosis factor α

Pharmacovigilance plan

Table 18 Ongoing and planned studies in the PhV development plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
Registries • ARTIS (RA0021) • RABBIT (RA0020) • NDB (RA0005) • BSRBR (RA0022) (Category 3)	Details of the objectives for each registry are described in Module SV of the RMP	In general, registries capture events related to important identified and potential risks.	Ongoing	Ongoing, final reports to be provided by 31 Jul 2018, except for BSRBR anticipated by 31 May 2019
Pregnancy • Ongoing studies • Post marketing reports • Registries (ARTIS, RABBIT) (Category 3)	To gather pregnancy data in a proactive and systematic way	Missing information Pregnancy and lactation Children and adolescents	Ongoing	Data will be provided concomitantly with the PSURs
AS001 Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in subjects with active axial spondyloarthritis (axial SpA) (Category 3)	Provide data on long-term use of CZP in axial spondyloarthritis subjects up to 204 weeks of treatment and a Safety Follow-Up Visit 10 weeks after their last dose of study medication	Missing information Long-term use in axial spondyloarthritis	Ongoing	The Week 48 interim report is in preparation, and the final complete report is planned for Q2 2016

Risk minimisation measures

Table 19 Summary table of risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks		
Infections including TB and serious opportunistic infections	• SmPC Section 4.8: addresses the risk of infections and its characteristics • SmPC Section 4.4: includes Special warnings and precautions for use • SmPC Section 4.4: includes a warning statement to perform screening tests for TB prior to initiating therapy, as well as appropriate anti-TB treatment in cases of latent TB infection. • SmPC Section 4.3: includes active TB and other severe infections as Contraindications	Educational program including HCP and patient surveys to assess the educational materials
Moderate to severe congestive heart failure (NYHA class III/IV)	• SmPC Section 4.8: addresses the risks of CHF and cardiac ischemic events and their characteristics • SmPC Section 4.4: includes Special warnings and precautions for use • SmPC Section 4.3: includes moderate to severe heart failure under Contraindications	Educational program including HCP and patient surveys to assess the educational materials
Hypersensitivity reactions	• SmPC Section 4.4 : includes Special warnings and precautions for use • SmPC Section 4.3: includes hypersensitivity reactions as Contraindications	Educational program including HCP and patient surveys to assess the educational materials
Malignancies including lymphoma, leukemia, Merkel cell carcinoma, Hepatosplenic T-cell lymphoma, and melanoma	• SmPC Section 4.8: addresses the risk of malignancies, including lymphoma, leukemia, Merkel cell carcinoma, and melanoma, and its characteristics • SmPC Section 4.4: includes Special warnings and precautions for use	Educational program including HCP and patient surveys to assess the educational materials
Demyelinating-like disorders	• SmPC Section 4.4: includes Special warnings and precautions for use	None
Aplastic anemia, neutropenia, thrombocytopenia, pancytopenia, and leukopenia	• SmPC Section 4.8: addresses the risks of anemia, neutropenia, thrombocytopenia, leukopenia, and pancytopenia, and their characteristics • SmPC Section 4.4: includes Special warnings and precautions for use	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Lupus and lupus-like illness	• SmPC Section 4.8: addresses the risk of autoimmune disorders and its characteristics • SmPC Section 4.4: includes Special warnings and precautions for use	None
Immunogenicity including sarcoidosis	• SmPC Section 5.1: addresses the risk of immunogenicity and its characteristics • SmPC Section 4.8: includes sarcoidosis in the table of adverse drug reactions	None
New onset or worsening of psoriasis (including palmoplantar pustular psoriasis) and related conditions	• SmPC Section 4.8: includes the risk of new onset or worsening of psoriasis (including palmoplantar pustular psoriasis) and related conditions in the table of adverse drug reactions	None
Hepatobiliary events including hepatitis, hepatic enzyme increased, and cholestasis	• SmPC Section 4.8: includes the risk of hepatobiliary events including hepatitis, hepatic enzyme increased, and cholestasis in the table of adverse drug reaction • SmPC Section 4.2: includes information on risk of use in patients with hepatic impairment	None
Important potential risks		
Ischemic cardiac events	• SmPC Section 4.8: addresses the risks of cardiac ischemic events	None
Serious bleeding events	• SmPC Section 4.4: includes Special warnings and precautions for use, and describes the aPTT assay interaction and explains the use of caution in the interpretation of abnormal coagulation test results	Educational program including HCP and patient surveys to assess the educational materials
Hepatitis B virus reactivation	• SmPC Section 4.4: includes Special warnings and precautions for use to perform screening tests for HBV prior to initiating therapy, and monitoring during treatment and for several months following termination of therapy	Educational program including HCP and patient surveys to assess the educational materials
Missing information		
Pregnancy and lactation	• SmPC Section 4.6: addresses the risk of use during pregnancy and lactation • SmPC Section 4.6: addresses the increased risk for infection in an infant whose mother was treated with CZP during pregnancy • SmPC Section 4.8: addresses pregnancy outcome risk (spontaneous abortion)	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Children and adolescents	• SmPC Section 4.2: includes information on risk of use in children and adolescents • SmPC Section 4.6: addresses the increased risk for infection in an infant whose mother was treated with CZP during pregnancy	None
Elderly	• SmPC Section 4.2 and Section 4.4: includes information on the risk of use in elderly patients	None
Patients with renal or hepatic impairment	• SmPC Section 5.2: includes PK properties • SmPC Section 4.2: describes the absence of data on Patients with renal or hepatic impairment	None
Potential for overdose	• SmPC Section 4.9: includes a description on the risk of overdose	None. The risk of overdose has been extremely minimal to date.
Potential for medication errors	• SmPC Section 4.2: the text is proposed to be separated into 2 parts: loading dose and maintenance dose in order to enhance clarity and ensure that the loading dose is correctly administrated. The review of the proposed text is ongoing as part of the PSUR6 assessment	An educational program serves to minimize the risks of erroneous administration by clearly describing the method of administration and the amount to be administered. The program includes HCP and patient surveys to assess the educational materials.
Off label use	• SmPC Section 4.1: includes therapeutic indications	None
Concomitant use with DMARDs other than MTX	• SmPC Section 4.5: includes information on risk of use with DMARDs other than MTX	None
Previous use of anti TNF therapy	• SmPC Section 4.4 includes the following text: There are limited data on the use of Cimzia in patients who have experienced a severe hypersensitivity reaction towards another TNF antagonist; in these patients caution is needed	None
Vaccination	• SmPC Section 4.4: includes Special warnings and precautions for use • SmPC Section 4.6: addresses the increased risk for infection in an infant whose mother was treated with CZP during pregnancy	Educational program including patient surveys to assess the educational materials
Long-term use in axial spondyloarthritis	• The safety risk of CZP in long-term use in axial spondyloarthritis is yet to be elucidated (per proposed EU SmPC).	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures

aPTT=activated partial thromboplastin time, CHF=congestive heart failure, DMARDs=disease modifying antirheumatic drugs, HBV=hepatitis B virus, HCP=health care professional, MTX=methotrexate, NYHA=New York Heart Association, PK=pharmacokinetic, SmPC=Summary of product characteristics, TB=tuberculosis, TNF=tumor necrosis factor

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1of the SmPC have been updated (**addition**; ~~deletion~~). The Package Leaflet has been updated accordingly.

4.1 Therapeutic indications

[…]

Axial spondyloarthritis

Cimzia is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising:

Ankylosing spondylitis (AS)

Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Axial spondyloarthritis without radiographic evidence of AS

Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to NSAIDs.

4.2 Posology and method of administration

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of **conditions for which Cimzia is indicated** ~~rheumatoid arthritis~~. Patients should be given the special alert card.

Posology

Loading dose

The recommended starting dose of Cimzia for adult patients ~~with rheumatoid arthritis~~ is 400 mg (**given** as 2 **subcutaneous** injections of 200 mg each ~~on one day~~) at weeks 0, 2 and 4~~, followed by a maintenance dose of 200 mg every 2 weeks~~. **For rheumatoid arthritis,** MTX should be continued during treatment with Cimzia where appropriate.

Maintenance dose

Rheumatoid arthritis

After the starting dose, the recommended maintenance dose of Cimzia for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. MTX should be continued during treatment with Cimzia where appropriate.

Axial spondyloarthritis

After the starting dose, the recommended maintenance dose of Cimzia for adults patients with axial spondyloarthritis is 200 mg every 2 weeks or 400 mg every 4 weeks.

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

Missed dose

Patients who miss a dose should be advised to inject the next dose of Cimzia as soon as they remember and then continue injecting subsequent doses ~~every 2 weeks~~ as originally instructed.

[...]

4.8 Undesirable effects

[...]

Axial spondyloarthritis

Cimzia was studied in 325 patients with active axial spondyloarthritis in a placebo-controlled clinical trial (AS001) for up to 30 months. The safety profile for axial spondyloarthritis patients treated with Cimzia was consistent with the safety profile in rheumatoid arthritis and previous experience with Cimzia.

[...]

Creatine phosphokinase elevations

The frequency of creatine phosphokinase (CPK) elevations was generally higher in patients with axSpA as compared to the RA population. The frequency was increased both in patients treated with placebo (2.8% vs 0.4% in axSpA and RA populations, respectively) as well as in patients treated with Cimzia (4.7% vs 0.8% in axSpA and RA populations, respectively). The CPK elevations in the axSpA study were mostly mild to moderate, transient in nature and of unknown clinical significance with no cases leading to withdrawal.

5.1 Pharmacodynamic properties

See SmPC for details.

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Cimzia 200 mg solution for injection. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In study AS001, 200 mg Q2W and 400 mg Q4W was tested in comparison to placebo during a 24 week period. The primary efficacy endpoint, the ASAS20 response at Week 12 was statistically significantly greater ($p<0.004$ and $p<0.001$) in both active groups (CZP 200mg Q2W [57.7%] and CZP 400mg Q4W [63.6%]) compared with the placebo group (38.3%). The differences to placebo (19.3% in the 200mg Q2W group and 25.2% in the Q4W group) are clinically relevant. Further, also the secondary endpoint ASAS40, which is considered more relevant for an anti-TNF agent, was met for both dosing groups, with a difference to placebo of approximately 30% at week 12 and slightly higher at week 24. Other secondary analyses also support the observed efficacy of CZP in axSpA (ASAS5/6, ASAS partial remission, PtGADA, total back pain NRS, BASFI, BASDAI 5 and 6, BASDAI, and BASDAI fatigue NRS) . Spinal mobility was significantly improved as evidenced by improvement in BASMI linear scores compared to placebo-treated patients. Significant inhibition of inflammatory signs in both sacroiliac joints and the spine was also observed in all doses group, in the overall axSpA population as well as in the AS sub-populations and nr-axSpA. Thus, the study results support the efficacy of CZP for both dosing groups in the overall AxSpA population, regarding sign and symptoms, physical function, pain, health-related quality of life, productivity, spinal mobility and inflammation.

Uncertainty in the knowledge about the beneficial effects

To further study the need for continuous anti-TNF therapy for axSpA patients to maintain clinical response or remission over time, the MAH will conduct a post-authorisation randomized controlled remission-withdrawal-retreatment study in early axSpA patients which is endorsed by the CHMP. The study will provide information about the proportion of subjects with early axSpA and who maintain their low disease activity state for an additional 48 weeks following drug withdrawal or dose reduction. The study will also collect information on safety and efficacy of re-treatment after disease flare. The MAH will provide the results of this study by January 2019.

Risks

Unfavourable effects

No new safety signal has emerged in study AS001. Comparisons were made to the RA safety databases. The safety profile for axSpA patients was consistent with the safety profile in RA and previous experience with CZP, with the exception of CPK elevations which were generally higher in patients with axSpA as compared to the RA population. This observation was reflected in section 4.8 of the SmPC. There were three cases of pustular psoriasis reported in the study AS001. The MAH will follow-up and report all cases of pustular psoriasis per indication and CPK elevations in the future PSURs. Elevated CPK and pustular psoriasis are both are already labelled as uncommon ADRs in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

The safety profile of CZP is well established and is characterised by several potentially serious risks, including but not limited to infections and potential risks of malignancies, congestive heart failure and demyelinating disorders. These serious risks have not been observed in study AS001. As described in

the RMP, these risks are monitored through extensive ongoing follow up programs (including registries) in rheumatologic diseases with focus on RA; in which long term safety data is collected and reported annually for several years. As described in the RMP the MAH will submit the final study report of study AS001 by Q2 2016 which will bring additional data on the long term safety of CZP in the treatment of axSpA patients.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Patients with axSpA, including AS and nr-axSpA, can now be classified by the ASAS classification criteria for axSpA. The ASAS classification criteria allows classification of axSpA in the absence of any imaging evidence of sacroiliitis, provided HLA B-27 is present together with 2 clinical parameters (i.e. nr-axSpA). Today, this group is primarily treated with NSAID, but the effect is sometimes not adequate, and the medication carries a risk for adverse events and intolerance. It is acknowledged that there is a medical need for treatment of these patients. AxSpA is a painful condition with a considerable negative impact on function and work productivity for the patients, regardless of subgroup, i.e. AS or nr-axSpA. CZP has shown a clinically relevant effect on both symptoms and function in patients with axSpA (including AS and nr-axSpA) and can provide an alternative for patients who do not respond adequately or are intolerant to NSAIDs.

The safety profile of CZP is well established. Treatment with CZP is connected with several potentially serious risks. In Study AS001 the most common AE was non serious infections, such as nasopharyngitis. No new safety signal has been identified in the AxSpA clinical development program submitted. The safety profile of CZP in the treatment of AxSpA appeared to be similar with the one known for the RA indication. Pustular psoriasis and elevated CRP will be closely followed-up in the future PSURs.

Benefit-risk balance

The MAH showed a robust effect of CZP treatment in the studied axSpA patient population and this is of clinical relevance in terms of symptomatic treatment. The safety profile of CZP in the studied population did not differ from the established safety profile of CZP in the RA indication. AxSpA patients who are candidates for CZP treatment must have severe active disease, inadequate response to or intolerance to NSAIDs, and for the nr-axSpA subpopulation, evidence of inflammation by elevated CRP and/or MRI. Requiring an objective measure of inflammation reduces the potential to treat patients with no inflammatory back pain.

In conclusion, based on the available efficacy and safety data presented, the benefit risk balance of CZP is considered positive for the treatment adult patients with severe active axSpA, comprising AS*:* adults with severe active AS who have had an inadequate response to, or are intolerant to NSAIDs; and nr-axSpA: adults with severe active axSpA without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to NSAIDs.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type
C.1.6 a)	Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication to include the treatment of adult patients with severe active axial spondyloarthritis, comprising: Ankylosing spondylitis (AS): Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs); and *Axial spondyloarthritis without radiographic evidence of AS:* Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to NSAIDs. Sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated accordingly as well as the package leaflet.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted anually until renewal.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe/use Cimzia are provided with a physician information pack containing the following:

- The Summary of Product Characteristics
- Physician information
- Patient Alert Card

The physician information should contain the following key messages:

- The risk of serious infections, including opportunistic bacterial, viral and fungal infections in patients treated with Cimzia,
- The need to evaluate patients for both active and inactive tuberculosis prior to starting the treatment, including use of appropriate screening tests,
- The contraindication of Cimzia in patients with history of moderate to severe heart failure (NYHA III/IV), and potential risk of congestive heart failure being worsened by Cimzia,
- The risk of acute injection-related reactions and delayed serious systemic hypersensitivity reactions, the need for instructing patients on techniques for administration, and guidance for Health Care Professionals on how to report administration errors,
- The role and use of patient alert card.