A 52-Week Randomized Placebo-Controlled Trial of Certolizumab Pegol in Patients with Non-Radiographic Axial Spondyloarthritis

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This supplement contains the following items:

PROTOCOL AS0006

PHASE 3, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO EVALUATE EFFICACY AND SAFETY OF CERTOLIZUMAB PEGOL IN SUBJECTS WITH ACTIVE AXIAL SPONDYLOARTHRITIS (AXSPA) WITHOUT X-RAY EVIDENCE OF ANKYLOSING SPONDYLITIS (AS) AND OBJECTIVE SIGNS OF INFLAMMATION

PHASE 3

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SERIOUS ADVERSE EVENT REPORTING

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ABA	abatacept
ACR	American College of Rheumatology
ADA	adalimumab
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
Anti-CZP Ab	anti-CZP antibody
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASAS20, 40	Assessment in Axial SpondyloArthritis International Society 20%, 40% response criteria
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASDAS-CII	Ankylosing Spondylitis Disease Activity Score clinically important improvement
ASDAS-HD	Ankylosing Spondylitis Disease Activity Score high disease activity
ASDAS-ID	Ankylosing Spondylitis Disease Activity Score inactive disease
ASAS-MD	Ankylosing Spondylitis Disease Activity Score moderate disease
ASDAS-MI	Ankylosing Spondylitis Disease Activity Score major improvement
ASDAS-vHD	Ankylosing Spondylitis Disease Activity Score very high disease activity
ASQoL	Ankylosing Spondylitis Quality of Life
ASspiMRI-a	Ankylosing spine MRI acuity
axSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMO	bone marrow oedema
BMP	bone morphogenetic protein
BOCF	Baseline observation carried forward
CDMS	clinical data monitoring system
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COX-2	cyclooxygenase 2
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products

CRF	case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CSF-1	colony-stimulating factor-1
CZP	certolizumab pegol
Dhh	Dessert hedgehog
DKK1	Dickkopf-related protein 1
DMARD	disease-modifying antirheumatic drug
DS	Drug Safety
ECG	electrocardiogram
eCRF	electronic Case Report Form
ePRO	electronic patient reported outcome
EQ-5D	EuroQoL Health Status Questionnaire (5 dimensions)
ES	Enrolled Set
ETN	etanercept
EU	European Union
FAS	Full Analysis Set
FU	Follow-Up
GCP	Good Clinical Practice
GM-CSF	granulocyte macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
GOL	golimumab
HCQ	hydroxychloroquine
HIV	human immunodeficiency virus
HLA-B27	human leukocyte antigen B27
HRQoL	health-related quality of life
ia	intra-articular
IB	Investigator Brochure
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFX	infliximab
IGRA	Interferon-Gamma Release Assay
Ihh	Indian hedgehog

IL	interleukin
IMP	investigational medicinal product
IP	interphalangeal
IRB	Institutional Review Board
iv	Intravenous(ly)
IXRS	interactive response system
LOCF	last observation carried forward
LTB	latent tuberculosis
M-CSF	Macrophage colony-stimulating factors
MASES	Maastricht Ankylosis Spondylitis Enthesitis Score
MCID	minimal clinically important difference
MCP	metacarpophalangeal
MCS	Mental Component Summary
MedDRA®	Medical Dictionary for Regulatory Activities®
MMP-3	matrix metalloproteinase-3
MMRM	mixed model for repeated measures
MOS	Medical Outcomes Study
MRI	magnetic resonance imaging
mNY	Modified New York (criteria)
MTX	methotrexate
nr-axSpA	nonradiographic axSpA
NRS	Numerical Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
NTMB	nontuberculous mycobacteria
NYHA	New York Heart Association
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PCS	Physical Component Summary
PFS	prefilled syringe
PhGADA	Physician's Global Assessment of Disease Activity
PGADA	Patient's Global Assessment of Disease Activity
PIP	Proximal IP
PK	pharmacokinetics
PPS	Per Protocol Set
prn	as needed

PsA	psoriatic arthritis
Q2W	every 2 weeks (every other week)
Q12W	every 12 weeks
QoL	Quality of Life
RA	rheumatoid arthritis
RDC	remote data capture
RS	Randomized Set
SAA	Spondylitis Association of America
SAARD	slow-acting antirheumatic drug
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
sCSF1r	soluble colony-stimulating factor-1 receptor
SD	standard deviation
SF-36	Short-Form 36-Item Health Survey
Shh	Sonic hedgehog
SI	sacroiliac
SIJ	sacroiliac joint injection
SOP	standard operating procedure
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SPARTAN	Spondyloarthritis Research and Treatment Network
SPC	Summary of Product Characteristics
SS	Safety Set
SSCM	Single Safety Case Management
SSZ	sulfasalazine
STIR	short-tau-inversion recovery
TB	tuberculosis
TGF	transforming growth factor
TNF	tumor necrosis factor
TNFi	tumor necrosis factor-alpha inhibitor
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal (for CRP the ULN defined as the upper limit of normal value indicative for inflammatory disease)
USA	United States of America

VAS	visual analog scale
VEGF	vascular endothelial growth factor
VU	vertebral units
WBC	white blood cell
WD	Withdrawal
wdt	withdrawal treatment
WISP	wingless-related mouse mammary tumor virus integration site protein (WNT1)-inducible signaling pathway proteins
WNT1	wingless-related mouse mammary tumor virus integration site protein
WPS	Work Productivity Survey

1 SUMMARY

AS0006 is a randomized, double-blind, parallel-group, placebo-controlled study, consisting of 52 weeks of treatment with certolizumab pegol (CZP) and a Follow-Up (FU) Period of 8 weeks after the Week 52 visit. The study population is subjects with active axial spondyloarthritis (axSpA) without x-ray evidence of ankylosing spondylitis (AS), but either with sacroiliitis on magnetic resonance imaging (MRI) or C-reactive protein (CRP) levels indicative of inflammatory disease or both, who have had an inadequate response to, have a contraindication to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

The study population will be subjects (≥18 years), with a documented diagnosis of adult-onset axSpA as meeting the Assessment of SpondyloArthritis International Society ([ASAS], Sieper et al, 2009) criteria of at least 12 months' symptom duration, and with active disease defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and spinal pain ≥4 on a 0 to 10 Numerical Rating Scale (NRS). At Baseline, evidence of inflammatory disease will be confirmed either by presence of sacroiliitis on MRI (according to ASAS/Outcome Measures in Rheumatology Clinical Trials [OMERACT] criteria) or by elevated CRP or by presence of both.

Additionally, subjects must have had an inadequate response to, have a contraindication to, or have been intolerant to at least 2 NSAIDs. Inadequate response to a NSAID is defined as lack of response to at least 14 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID. Eligible subjects will be allocated to the following study treatments in a 1:1 ratio:

- CZP administered subcutaneously (sc) at the dose of CZP 400mg at Weeks 0, 2, and 4 followed by CZP 200mg every 2 weeks (every other week; Q2W) sc (starting at Week 6)
- Placebo

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), study treatments will be administered sc at the study site by dedicated, unblinded, and adequately trained site personnel. The study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. All subjects will receive training for self-injection at the study site at Weeks 10 and 12. During the training at the Weeks 10 and 12 visits, the study treatment will be self-administered under the supervision of the dedicated unblinded study personnel.

The study will be placebo controlled for 52 weeks and will allow changes in background medications as required to control disease activity according to the judgment of the Investigator.

Subjects whose disease activity cannot be controlled by study medication and changes in background therapy (including and not limited to analgesics, NSAIDs, and slow-acting antirheumatic drug [SAARDs]) will be permitted to withdraw from the double-blind study drug. Subjects will either transition to open-label treatment offered by UCB with the marketed product of CZP, after Week 52, ie, completion of all study assessments, or at the discretion of the Investigator and in accordance with the local regulatory requirements for a maximum duration of 2 years or until marketing authorization is granted for CZP (if applicable), whichever comes first, or subjects will transition to receive other treatment (including biologics). These subjects will remain in the study until the assessment of the primary endpoint at Week 52.

All subjects, including those withdrawn from study treatment, will have a FU Visit 8 weeks after their final Week 52 visit.

If the Investigator chooses to withdraw subjects on the other treatments (including biologics), the local guidelines on initiation and monitoring of the particular treatment should be followed.

The primary objective of the study is to demonstrate the efficacy of CZP administered at the dose of CZP 200mg Q2W, after a loading dose of CZP 400mg at Weeks 0, 2, and 4, on the signs and symptoms of active axSpA in subjects without x-ray evidence of AS.

The secondary objectives of the study are to assess efficacy, safety, and tolerability and to demonstrate the effect of CZP on health outcomes, disease activity, sacroiliac (SI) joint inflammation through MRI, and changes in concomitant and background medications.

Other objectives are to evaluate the effects of CZP on spinal mobility, total and nocturnal spinal pain (NRS), spinal inflammation, SI joint structural changes, treatment response over time, additional signs and symptoms of the disease, subject's health status, acute phase reactant (CRP), health-related quality of life (HRQoL), work and household productivity, pharmacokinetics (PK) and immunogenicity, gene and protein expression and to explore the relationship between genomic biomarkers and disease biology, drug treatment and inflammatory and immune responses (for those subjects who consent to the genomics substudy).

The primary efficacy variable is Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) response at Week 52. The secondary efficacy variables are Assessment in Axial SpondyloArthritis International Society 40% (ASAS40) response at Weeks 12 and 52, change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Weeks 12 and 52, change from Baseline in BASDAI at Weeks 12 and 52, change from Baseline in Sacroiliac-Spondyloarthritis Research Consortium of Canada (SI-SPARCC) score at Week 12, and the number of subjects without relevant changes to background medication.

Other efficacy variables are listed in Section 4.1.3.

Pharmacokinetic/exploratory biomarker, and pharmacogenomic variables are listed in Section 4.2 and immunogenicity variables are listed in Section 4.3.

Safety variables to be assessed are adverse events (AEs), vital signs, physical examination, and measurements of laboratory parameters. In addition, subjects will be evaluated at Screening, Baseline, and at every 12 weeks thereafter up to and including Week 36 for signs and symptoms of latent or active tuberculosis (TB) infection and risk factors for exposure to TB using the TB questionnaire.

Approximately 900 subjects will be screened in order to have 300 subjects (150 subjects per treatment group) randomized into the study. Randomization will be stratified by presence of sacroiliitis on MRI and elevated CRP to ensure balanced treatment allocation across three subgroups: MRI+/CRP+; MRI+/CRP-; MRI-/CRP+. For each subject, the study will last a maximum of 66 weeks and will consist of 3 periods:

- Screening Period lasting up to 6 weeks
- Double-Blind, placebo-controlled Period for 52 weeks
- FU Period 8 weeks after the Week 52/Withdrawal (WD) visit.

The estimated recruitment period is up to 15 months. The first subject first visit is planned in Quarter 3 2015. A completed subject is one who completes the Week 52 Visit.

2 INTRODUCTION

2.1 Natural history of axial spondyloarthritis

Spondyloarthritis (SpA) is an umbrella term applied to a family of rheumatic diseases that have features in common with and distinct from other inflammatory arthritides, particularly rheumatoid arthritis (RA).

Recently, the ASAS working group established classification criteria to distinguish 2 broad categories of SpA: peripheral and axial SpA (axSpA) (Rudwaleit et al, 2011; Rudwaleit, 2010 Rudwaleit et al, 2009b). This division is based on the body part predominantly involved in the inflammatory process and those areas of the body that may respond similarly well to medication. Therefore, peripheral SpA includes diseases affecting mainly peripheral joints, such as reactive arthritis and psoriatic arthritis (PsA), whereas axSpA comprises those diseases with mainly axial involvement (SI joints and spine), including AS and nonradiographic axSpA (nr-axSpA).

Patients with AS have definitive evidence of structural changes in the sacroiliac joint (sacroiliitis) on x-ray, fulfilling the Modified New York classification criteria (mNY-positive) (van der Linden et al, 1984a), whereas those with nr-axSpA have no definitive structural changes on conventional radiographs (mNY-negative) (Rudwaleit et al, 2005; Dougados et al, 1991).

Axial SpA is a chronic inflammatory disease that impacts a substantial proportion of the population. Limited evidence exists regarding the exact prevalence of axSpA; however, recent data suggest that the prevalence is similar to that of RA in the United States of America (USA) (axSpA: 0.7% to 1.4%; RA: 0.5% to 1.0%) (Reveille et al, 2012; Myasoedova et al, 2010; Helmick et al, 2008).

The majority of patients with axSpA have inflammatory back pain. The disease typically originates in the sacroiliac joints, then progresses to the spine. In the sacroiliac joints and the spine, active inflammation results in erosions, sclerosis, and fatty lesions. However, the most characteristic feature is new bone formation leading to ankylosis of the sacroiliac joints and syndesmophytes attached to the vertebral bodies. As a result of extended syndesmophyte formation, the spine may become fused over time. Objective signs of inflammation, such as enthesitis, dactylitis, peripheral arthritis, or uveitis; genetic features, such as the presence of human leukocyte antigen B27 (HLA-B27); and laboratory parameters, such as elevated CRP, may also be present (Braun, 2012; Rudwaleit et al, 2009a; Braun and Sieper, 2007). Disability in axSpA is related to both the degree of inflammatory activity, causing pain, stiffness, fatigue, and poor quality of sleep, and to the degree of bony ankylosis, causing loss of spinal mobility.

The natural history of axSpA is characterized by a variable disease course. Over time, patients may develop structural damage or radiographic abnormalities involving their SI joints, and they may fulfill the mNY classification criteria for AS. However, the rate of development of structural damage varies among patients (Rudwaleit and Sieper, 2012). Some patients develop only unilateral sacroiliitis, and others may never develop definitive sacroiliitis on x-ray despite significant disease burden and other signs and symptoms of the disease, such as spinal lesions, uveitis, enthesitis, and peripheral arthritis. Approximately 10% of patients with nr-axSpA (25%

if CRP levels are elevated) develop definitive evidence of sacroiliitis on x-ray within 2 years (Sieper and van der Heijde, 2013a).

2.2 Burden of disease in axSpA

Axial SpA typically presents in patients <45 years of age, and these relatively young and otherwise healthy patients face a significant disease burden regardless of whether or not they have definitive evidence of sacroiliitis on x-ray. These patients experience substantial pain, prolonged, severe stiffness of joints, substantial sleep disturbances, reduced mobility and overall function, reduced quality of life (QoL), loss of productivity, and other disease-related symptoms (Huscher et al, 2006; Kobelt et al, 2006; Kobelt et al, 2004; Boonen et al, 2003; Boonen et al, 2002; Ward, 2002). Moreover, studies have shown that the economic impact of the disease on society or patients can be substantial and that the costs are mainly driven by the cost associated with loss of work capacity (van der Heijde et al, 2013; Kobelt et al, 2006; Kobelt et al, 2004, Boonen et al, 2003; Ward, 2002).

Several large observational and noninterventional cohort studies (Cuirea et al, 2013; Sieper and van der Heijde, 2013a) reported a similar burden of disease at study baseline across AS studies (captured through BASFI and BASDAI) in nonradiographic as well as radiographic axSpA (captured through BASDAI). A literature review of clinical studies in both populations (Callhoff et al, 2015) and (RAPID-AxSpA) (Landewe et al, 2014) confirmed this finding in the clinical study setting.

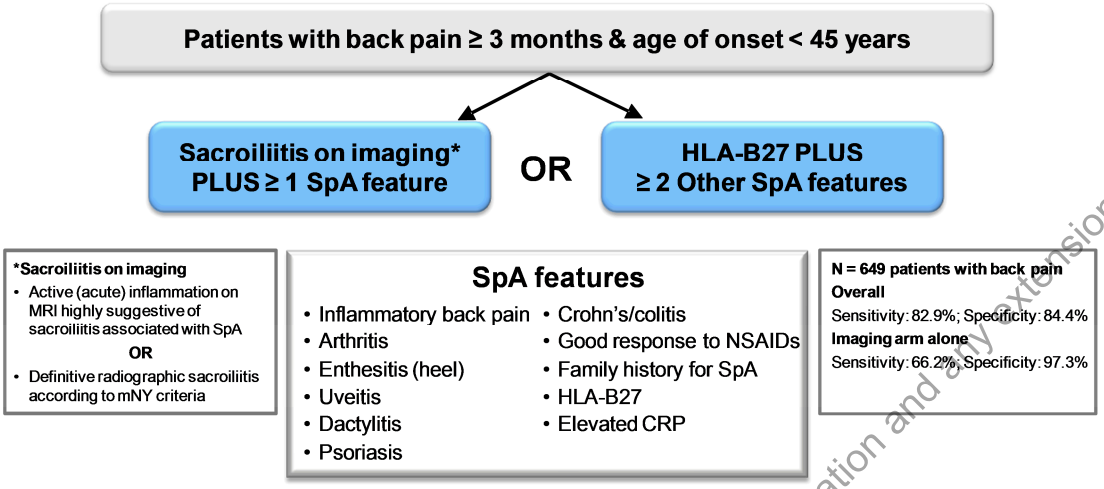
2.3 Diagnosing axSpA in clinical practice

The diagnosis of AS and/or axSpA should be based on clinical assessments considering typical signs and symptoms, but also excluding other diseases that may have similar presentations. The mNY classification criteria, often used to support the diagnosis of AS, excludes patients who do not show definitive evidence of sacroiliitis on x-ray (Rostom et al, 2010). For a definitive classification of AS, the mNY classification criteria require radiographic evidence of sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3 to 4 unilaterally PLUS at least 1 of the following clinical criteria: low back pain and stiffness for ≥3 months, limitation of lumbar spine motion, or limitation of chest expansion. These criteria were designed for classification of patients in clinical trials rather than for diagnostic purposes. However, they have historically been used for clinical diagnosis. The requirement for limitations in spinal motion and/or chest expansion has led to diagnoses being delayed until irreversible structural damage is documented on SI joint x-rays. Several publications have documented that time from symptom onset until the diagnosis of AS ranges from 5 years to 10 years (van der Linden et al, 1984b; Feldtkeller et al, 2003; Feldtkeller et al, 2000), thus demonstrating that x-ray changes lag far behind other signs and symptoms.

Due to the problem of delayed disease recognition, ASAS developed new classification criteria for axSpA that do not require the presence of definitive sacroiliitis on x-ray, thus identifying a nonradiographic subpopulation (nr-axSpA) allowing for classification of all axSpA patients (Rudwaleit et al, 2009b; Rudwaleit et al, 2009c). These criteria establish standards that apply to patients with or without radiographic sacroiliitis enabling the conduct of clinical trials in patients with both nr-axSpA and AS. In patients with a history of chronic back pain for ≥3 months and age of onset <45 years, classification of axSpA can be made based on either evidence of sacroiliitis on radiographs or MRI plus ≥1 typical SpA feature or the presence of HLA-B27 plus

≥2 typical SpA features (Figure 2–1). In these criteria, sacroiliitis is defined as MRI evidence of SI joint inflammation or radiographic evidence of sacroiliitis meeting mNY criteria (Rostom et al, 2010).

Figure 2–1: ASAS Classification Criteria for axSpA



ASAS=Assessment of SpondyloArthritis International Society; axSpA=axial spondyloarthritis; CRP=C-reactive protein; HLA-B27=human leukocyte antigen B27; mNY=modified New York; MRI=magnetic resonance imaging; NSAID=nonsteroidal anti-inflammatory drug; SpA=spondyloarthritis.
Adapted from Rudwaleit M, et al. *Ann Rheum Dis*. 2009; 68(6):777-783 (Rudwaleit et al, 2009c).

2.4 Current management of axial spondyloarthritis

There is increasing recognition of axSpA as an important clinical entity, as evidenced by the efforts of the American College of Rheumatology in cooperation with the Spondylitis Association of America (SAA) and the Spondyloarthritis Research and Treatment Network (SPARTAN) to develop new treatment recommendations for axSpA including AS (see Appendix 18.1 for classification criteria for axSpA). To help Investigators and at the same time reduce the introduction of bias in the study resulting from changes in background medications, UCB is recommending allowed changes in background therapy. These allowed changes were prepared by expert rheumatologists from North America and Europe and have also been aligned with the draft American College of Rheumatology (ACR)/SAA/SPARTAN Recommendations for the Management of Axial Spondyloarthritis, including Ankylosing Spondylitis, and Children with the Enthesitis-Related Arthritis Form of Juvenile Idiopathic Arthritis presented at the recent ACR Nov 2014 meeting in Boston. Furthermore, the update of the 2006 ASAS recommendations for the use of anti-tumor necrosis factor (TNFs) for ankylosing spondylitis extended the recommendations to patients fulfilling the ASAS criteria, including patients with nr axSpA (van der Heijde et al, 2011).

Nonsteriodal anti-inflammatory drugs are often rapidly effective for the symptoms (pain and stiffness) of axSpA (Poddubnyy, 2013; Poddubnyy et al, 2012), but many patients lose symptomatic response and structural damage often progresses despite their use. Conventional disease-modifying antirheumatic drugs (DMARDs; eg, methotrexate [MTX] and sulfasalazine [SSZ]) have limited efficacy in axial disease, but may benefit patients with peripheral joint disease (Haibel et al, 2007; Braun et al, 2006; Haibel et al, 2005). Therefore, DMARDs are

recommended only in patients with predominantly peripheral manifestations (Braun and van den Berg, 2011).

Patients who are intolerant of or have inadequately responded to NSAIDs, or those in whom NSAIDs are contraindicated, have limited treatment options. Tumor necrosis factor alpha (TNFα) inhibitors (CZP, adalimumab [ADA] etanercept [ETN] infliximab [IFX]), golimumab [GOL]) are currently the only effective and approved treatment options as of Dec 2014; IFX and GOL are indicated for active AS only, while CZP, ADA, and ETN are indicated for axSpA without radiographic evidence of AS (nr-axSpA) as an addition to the AS indication in several regions.

At the 2014 Annual Meeting of the ACR/SPARTAN group a draft treatment guideline was presented for the subject suffering from both AS and nr-axSpA. These guidelines recommend the use of a TNF inhibitor after NSAID treatment.

With the advent of the ASAS classification criteria for axSpA, several registration studies have been conducted in patients with nr-axSpA (Dougados et al, 2014), or axSpA (Landewe et al, 2014; Sieper et al, 2013b; Sieper et al, 2013c). These studies have shown that anti-TNFs are effective in nr-axSpA patients, particularly in patients with objective signs of inflammation as defined by MRI positivity or elevated CRP. The RAPID-axSpA study, the first axSpA study to enroll both AS and nr-axSpA patients in the same study, showed that baseline disease activity and treatment effect were similar between nr-axSpA and AS subjects (Landewe et al, 2014). In this study, it was shown that CZP rapidly reduced the signs and symptoms of axSpA disease over 24 weeks of Double-Blind treatment in the broad axSpA population, including the AS and the nr-axSpA subpopulations, and that the responses to the treatment were similar in both subpopulations (Landewe et al, 2014; Sieper and van der Heijde, 2013c) and maintained up to Week 96 (Mease et al, 2014; Sieper et al, 2014).

Based on the results of the RAPID-axSpA study, CZP received approval for the treatment of adult patients with severe active axSpA (comprising AS and nr-axSpA) in the European Union (EU) and several other countries, eg, Turkey, Argentina, Russia, Chile, Switzerland, Hong Kong, Dominican Republic, Ecuador, and Peru, and it was approved for the treatment of adults with active AS in the USA, Canada, Australia, and also Malaysia.

In accordance with the ASAS classification criteria a subject can either be classified as having axSpA based on imaging evidence or on clinical assessment. Recent publications showed that sacroiliitis on imaging via MRI is highly specific for the diagnosis of axSpA and is commonly used in many regions to diagnose axSpA in daily clinical practice (Rudwaleit et al, 2009a; Rudwaleit et al, 2009b; Rudwaleit et al, 2009c).

Because of the therapeutic response in early disease, the ASAS consensus recommendation on the use of TNFα inhibitors in AS, updated in 2010, was extended to include the full spectrum of axSpA (van der Heijde et al, 2011).

2.5 Rationale

The RAPID-axSpA study enrolled subjects with objective signs of inflammation, and the results indicated that baseline disease burden was similar between the AS and nr-axSpA subpopulations (Landewe et al, 2014; Sieper et al, 2013b). In the RAPID-AxSpA study it was shown that CZP rapidly reduced the signs and symptoms of axSpA over 24 weeks of double-blind treatment in

the broad axSpA population, including in the AS and the nr-axSpA subpopulations, and that the responses to the treatment were similar in both subpopulations (Landewe et al, 2014; Sieper et al, 2013b) and maintained up to Week 96 (Mease et al, 2014; Sieper et al, 2014).

To address the unmet need for treatment options for nr-axSpA, AS0006 will be conducted focusing on subjects who do not meet the mNY classification criteria for AS (see Appendix 18.2). Data suggest that patients with objective signs of inflammation and high disease activity are likely to run a chronic disease course and unlikely to be well managed on conventional therapy (Rudwaleit ACR 2013). Furthermore, studies where anti-TNFs have been withdrawn in nr-axSpA patients show that patients flare quickly and hence the disease is unlikely to go into spontaneous remission. However, there are no long-term prospective studies to assess how patients meeting the ASAS classification criteria respond to conventional therapies. With the conduct of this 52-week study comparing CZP to placebo in combination with standard of care, a better understanding should be gained of how a long-term anti-TNF therapy compares to standard of care in patients meeting the ASAS criteria with objective signs of inflammation. Moreover, patients whose disease cannot be managed under the blinded study treatment conditions will be able to discontinue study treatment and transition to either open-label CZP or other therapies.

Subjects enrolled into this study must have sacroiliitis on MRI as set forth by the ASAS/OMERACT definition; or meet the requirements for the clinical arm of the ASAS classification criteria for axSpA (MRI-negative nr-axSpA) and have elevated CRP levels, as there is good evidence to suggest that CRP is a predictor of response to anti-TNF therapy in axSpA.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of the study is to demonstrate the efficacy of CZP 200mg Q2W on the signs and symptoms of subjects with active axSpA without x-ray evidence of ankylosing spondylitis.

3.2 Secondary objective(s)

The secondary objectives of the study are to assess efficacy, safety, and tolerability and to demonstrate the effect of CZP on:

- Health outcomes
- Disease Activity
- SI joint inflammation through MRI
- Changes in concomitant and background medications

3.3 Other objectives

The other objectives of the study are to assess the effect of CZP on the following:

- Spinal mobility
- Total and nocturnal spinal pain (NRS)

- Spinal inflammation
- SI joint structural changes
- Treatment response over time
- Additional signs and symptoms of the disease
  - Morning stiffness
  - Fatigue
  - Extra-articular manifestations of axSpA
  - Sleep
  - Physical function
- Subject`s health status
- Acute phase reactant (CRP)
- HRQoL
- Work and household productivity
- Pharmacokinetics and immunogenicity
- Gene and protein expression and to explore the relationship between genomic biomarkers and disease biology, drug treatment and inflammatory and immune responses (for those subjects who consent to the genomics substudy).

4 STUDY VARIABLES

4.1 Efficacy variable(s)

4.1.1 Primary efficacy variable

- ASDAS-MI at Week 52

4.1.2 Secondary efficacy variables

The secondary efficacy variables are as follows:

- ASAS40 response at Weeks 12 and 52
- Change from Baseline in BASFI at Weeks 12 and 52
- Change from Baseline in BASDAI at Weeks 12 and 52
- Change from Baseline in SI-SPARCC score at Week 12
- Number of subjects without relevant changes to background medication

4.1.3 Other efficacy variables

The following variables will be analyzed at scheduled time points through Week 52:

- ASAS20, ASAS40, ASAS5/6, and ASAS partial remission response
- Change from Baseline in individual ASAS components:

  - Patient's Global Assessment of Disease Activity (PGADA)
  - Total and nocturnal spinal pain (NRS)
  - BASFI
  - Average of Questions 5 and 6 of the BASDAI concerning morning stiffness
  - Change from Baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) lateral spine flexion
  - CRP
- Change from Baseline in BASDAI and individual Questions 1, 2, 3 and 4
- Change from Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS)
- Change from BASMI linear
- ASDAS disease activity (Ankylosing Spondylitis Disease Activity Score inactive disease [ASDAS-ID], Ankylosing Spondylitis Disease Activity Score moderate disease [ASDAS-MD], Ankylosing Spondylitis Disease Activity Score high disease activity [ASDAS-HD], Ankylosing Spondylitis Disease Activity Score very high disease activity [ASDAS-vHD]) and clinical improvement (Ankylosing Spondylitis Disease Activity Score clinically important improvement [ASDAS-CII], ASDAS-MI)
- BASDAI 50 response
- Change from Baseline in Fatigue (NRS) (from BASDAI)
- Change from Baseline in sacroiliac SPARCC score at Week 52 and ankylosing spine MRI acuity (ASspiMRI-a) in the Berlin modification at Week 12 and Week 52
- Proportion of subjects with sacroiliac SPARCC score <2 at Week 12 and Week 52
- Change from Baseline in Ankylosing Spondylitis Quality of Life [ASQoL]
- Change from Baseline in ASAS-NSAID score
- Number of uveitis flares
- Number of inflammatory bowel disease (IBD) exacerbations
- Number of psoriasis exacerbations
- Work Productivity Survey (WPS)
- Change from Baseline in the Sleep Problems Index II domains of the Medical Outcomes Study [MOS] Sleep scale
- Change from Baseline in enthesitis (Maastricht Ankylosis Spondylitis Enthesitis Score [MASES])
- Change from Baseline in swollen and tender joint counts (44 joint count)
- Change from Baseline in Physician's Global Assessment of Disease Activity (PhGADA)

- Change from Baseline in the Short Form 36 Item Health Survey [SF-36], Physical Component Summary [PCS], and Mental Component Summary [MCS]
- Change from Baseline in the SF-36 domains:
  - Role Physical
  - Bodily Pain
  - General Health
  - Vitality
  - Social Functioning
  - Role Emotional
  - Mental Health
- Health status as assessed by the EuroQoL Health Status Questionnaire (5 dimensions) (EQ-5D) domains, visual analog scale [VAS] actual score and change from Baseline in VAS score
- Resources utilization: concomitant medical procedures, health care provider consultations not foreseen by the protocol, hospitalizations/emergency room visits

4.2 Pharmacokinetic, exploratory biomarker, and pharmacogenomic variables

4.2.1 Primary pharmacokinetic variables

Certolizumab pegol plasma concentrations will be measured at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52, and at the FU Visit (8 weeks after the Week 52/WD Visit).

These plasma samples may be used additionally for analyses of CZP and its constituent moieties using alternative methods.

4.2.2 Exploratory biomarkers variables

Selected samples collected for measurement of CZP plasma concentration may be used additionally for analyses of candidate exploratory biomarkers and cytokines, where appropriate. The biomarkers to be analyzed may include, but will not be limited to the following:

Matrix metalloproteinase-3 (MMP-3), bone morphogenetic protein (BMP)-2,-4 and -7, wingless-related mouse mammary tumor virus integration site protein (WNT1), inducible signaling pathway proteins (WISP), gremlin, dickkopf-related protein 1 (DKK1), sclerostin, hedgehog proteins (Sonic hedgehog [Shh], Indian hedgehog [Ihh], Dessert hedgehog [Dhh]), collagen turnover/cleavage products, collagen type X, vascular endothelial growth factor (VEGF), citrullinated vimentin fragments, cytokines: interleukin 13 [IL13], interleukin 17A and F [IL17 A and IL17 F], interleukin23 [IL23], interleukin34 [IL34], transforming growth factor (TGF) β, macrophage colony-stimulating factors (M-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), CSF-1, and soluble CSF-1 receptor (sCSF1r) levels.

4.2.3 Pharmacogenomic variables

For individuals consenting to the genomics substudy, blood samples will be drawn for possible genetic/epigenetic, genomic, proteomic, and metabolomics analysis at Baseline and Week 12. Additional samples will be collected for genomics, proteomics, and metabolomics analysis only, at Baseline, Weeks 4, 12, and 52. Collection of the samples will enable the exploratory evaluation of biomarkers relative to disease activity, drug treatment, and inflammatory and immune response processes. The nature and format of these tentative analyses will be determined when the results of the main study are made available. The samples will be stored at -80°C at the central biorepository for up to 20 years.

4.3 Immunological variable(s)

Anti-CZP antibody (anti-CZP Ab) concentrations will be assessed at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52, and the FU Visit (8 weeks after the Week 52/WD Visit). In addition, the anti-CZP Ab concentrations will be assessed in subjects who withdraw from study drug and transition to open-label CZP. The number and percent of subjects with anti-CZP Ab concentrations above 2.4 units/mL will be reported as follows:

- Number and percentage of subjects with anti-CZP Ab >2.4 units/mL at the time of each visit
- Number and percentage of subjects with anti-CZP Ab >2.4 units/mL at any visit during treatment (not including posttreatment withdrawal or FU visits)
- Number and percentage of subjects with anti-CZP Ab >2.4 units/mL at any visit including posttreatment withdrawal or FU visits

4.4 Safety variables

Safety variables to be assessed are physical examinations, AEs, vital signs, and measurements of laboratory parameters.

Adverse events will be solicited at every visit, and recorded and coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA®) criteria.

Physical examination findings will be recorded in the case report form (CRF) only at Screening. Clinically important abnormal changes in subsequent physical examinations will be recorded as AEs at all visits from Baseline to the FU Visit.

Clinical laboratory values (hematology, biochemistry, urinalysis) will be collected and assessed at Screening, Baseline, Weeks 2, 4, 8, 12, 24, 36, at the end of study Completion at Week 52/Early Withdrawal Visit and at the FU Visit (8 weeks after the Week 52/WD Visit). In addition, clinical laboratory values will be collected and assessed at study visits during the administration of open-label CZP in subjects who withdraw from the study treatment.

Furthermore, CRP will be collected and assessed either in a blinded or open manner at Screening, 3 to 5 days before Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and at the end of study Completion at Week 52/Early Withdrawal Visit and at the FU Visit (8 weeks after the Week 52/WD Visit).

At Screening, all subjects will have an Interferon-Gamma Release Assay (IGRA) test (QuantiFERON® TB test or Elispot®test, when the QuantiFERON test indicated is not available), and a chest x-ray read (or, if done, computed tomography of the chest) which must be reported

consistent with standard clinical reporting practice by an experienced qualified TB specialist, radiologist, or a pulmonologist, who is specifically required to look for signs of active TB or signs of past/inactive TB infection. The official report of the imaging must specifically indicate the absence of findings suggestive of current active TB or prior inactive TB. In addition to a physical examination done intermittently throughout the study, subjects will be evaluated at Screening, Baseline, and every 12 weeks thereafter up to and including Week 36, including the Completion/Early Withdrawal Visit, for signs and symptoms of latent or active TB infection and risk factors for exposure to TB using the TB questionnaire.

5 STUDY DESIGN

5.1 Study description

Study AS0006 is a 52-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study to evaluate the efficacy and safety of CZP in adult subjects with active axSpA without x-ray evidence of ankylosing spondylitis and with objective signs of inflammation (sacroiliitis on MRI and/or elevated CRP) and who have had an inadequate response to, have a contraindication to, or are intolerant to NSAIDs.

5.1.1 Study periods

The study includes 3 periods. An injection schedule is provided in Section 7.2.2.

Period 1 (Screening Period): 1 to 6 weeks before Baseline.

Prior to any study activities, subjects will be asked to read and sign the Informed Consent form for the conduct of the study. A separate informed consent form will also be obtained from subjects consenting to the use of their blood samples in a substudy for possible genetic, genomic/epigenetic, and proteomic analysis.

Laboratory data is to be obtained to verify the doses of MTX, SSZ, hydroxychloroquine (HCQ), NSAIDs, and corticosteroids, if used, are stable. Laboratory data will also be collected to ensure the washout of any medications not permitted for use during the study has been performed, and to initiate latent TB treatment where necessary. Concomitant medications permitted during the study should remain stable for at least 4 weeks prior to Baseline.

Sacroiliac-joint x-ray (not older than 12 months before Baseline and verified by central reading during the Screening Period) must prove that the subject belongs to the mNY-negative axSpA subpopulation, ie, does not have sacroiliitis grade ≥2 bilaterally or grade 3 to 4 unilaterally. Potentially eligible axSpA subjects without suitable SI-joint x-ray must undergo the x-ray with central reading within the Screening Period. SI-joint x-rays (read centrally) will allow discrimination of subjects with AS and without definitive evidence for sacroiliitis on x-ray (mNY negative-axSpA). Subjects with AS (mNY-positive) must be excluded from further participation in this study.

Confirmed mNY-negative axSpA subjects must undergo an MRI later during the Screening Period for central reading with results from the central reading available by no later than at the Baseline visit.

Additionally the subjects must get a further measurement of CRP 3 to 5 days before Baseline (Week 0).

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

Eligible subjects will be allocated to the following study treatments in a 1:1 ratio:

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

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), study treatments will be administered sc at the study site by dedicated, unblinded and adequately trained site personnel. The study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. All subjects will receive training for self-injection at the study site on Weeks 10 and 12. During the training on Weeks 10 and 12 visits, the study treatment will be self-administered under the supervision of the unblinded study personnel. Concomitant medications permitted during the study should remain stable for at least 4 weeks prior to the Week 12, 24, and 52 assessments.

Period 3 (Follow-Up Period):

All subjects, including those withdrawn from study treatment, will have a FU Visit 8 weeks after the Week 52/WD visit.

Alternative schedules

Subjects who discontinue the study treatment and enter open-label treatment with CZP or other treatments (including biologics) will follow alternative schedules of assessments. Assessments are to be continued as at Week 12 every 12 weeks until as close as possible to Week 52 (within ±4 weeks of the originally planned Week 52 Visit) of the regular visit schedule. Subjects will then be invited to the final assessment visit at Week 52.

5.1.2 Study duration per subject

For each subject, the study will last a maximum of 66 weeks, as follows:

- Up to 6 weeks in the Screening Period
- 52 weeks in the Double-Blind Period
- A FU Visit 8 weeks after the Week 52/WD visit

The estimated recruitment period is up to 15 months. The first subject first visit is planned in Quarter 3 of 2015. A completed subject is one who completes the Week 52 Visit. UCB will offer continuation of open-label treatment with the marketed product of CZP, after Week 52, ie, completion of all study assessments, on discretion of the Investigator and in accordance with the local regulatory requirements, for a maximum duration of 2 years or until marketing authorization is granted for CZP (if applicable), whichever comes first.

5.1.3 Planned number of subjects and site(s)

Approximately 900 subjects are expected to enter the Screening Period in order to have 300 subjects randomized into the Double-Blind Period. The end of the study will be defined as the date of last subject last FU Visit. It is planned to enroll the subjects at approximately 95 sites.

5.1.4 Anticipated regions and countries

The study will be conducted in North America, Australia, Europe, Asia, and other regions as appropriate.

5.2 Schedule of study assessments

The Schedule of assessments is shown in Table 5–1 for subjects who complete the study on either CZP 200mg Q2W or placebo.

In order to optimize the treatment the Investigator may adjust the background medication in accordance with the specifications described in Table 7–1.

At any time during the study course, but preferably not before Week 12, the Investigator may discontinue the study treatment and start open-label treatment with either CZP (which will be provided free of charge by UCB) or an alternative drug (eg, other treatment [including biologics]). Table 5–2 shows the Schedule of assessments for subjects receiving open-label treatment with CZP and Table 5–3 for subjects receiving an alternative treatment (not CZP).

Table 5–1: Schedule of study assessment - Study Periods 1 to 3 (Screening until FU)

Visit #	**Scr**	**Scr day -5 to-3**	**1/BL**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9H**	**10**	**11H**	**12**	**13H**	**14**	**15H**	**16**	**17H**	**18**	**19H**	**20**	**21H**	**22**	**23H**	**24**	**25H**	**26**	**27**	**28**	**29**
Week Protocol Activity	**-6 to -1**		**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14/H**	**16**	**18/H**	**20**	**22/H**	**24**	**26/H**	**28**	**30/H**	**32**	**34/H**	**36**	**38/H**	**40**	**42/H**	**44**	**46/H**	**48**	**50**	**52/WD**	**FU[b]**
Inclusion/ Exclusion criteria	X	X	X																												
Informed consent[a]	X																														
Demographic data	X																														
Medical history and procedure history (incl. axSpA history)	X																														
Vital signs[c]	X		X		X	X	X	X	**X**	X		X		X		X		X		X		X		X		X		X		X	X	X	X
Haematology/ urine/ biochemistry/	X[d]		X		X	X		X		X						X						X								X	X
CRP	X[e]	X			X	X		X		X		X		X		X		X		X		X		X		X		X		X	X
Pregnancy testing[f]	X		X																											X	X
PE[g]	X		X		X	X		X		X		X				X						X								X	X
Extra-articular assessments			X			X				X						X						X						X		X	
Chest x-ray[h]	X																													X	
TB test[i]	X																													X	

Table 5–1: Schedule of study assessment - Study Periods 1 to 3 (Screening until FU)

Visit #	**Scr**	**Scr day -5 to-3**	**1/BL**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9H**	**10**	**11H**	**12**	**13H**	**14**	**15H**	**16**	**17H**	**18**	**19H**	**20**	**21H**	**22**	**23H**	**24**	**25H**	**26**	**27**	**28**	**29**
Week Protocol Activity	**-6 to -1**		**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14/H**	**16**	**18/H**	**20**	**22/H**	**24**	**26/H**	**28**	**30/H**	**32**	**34/H**	**36**	**38/H**	**40**	**42/H**	**44**	**46/H**	**48**	**50**	**52/WD**	**FU[b]**
TB questionnaire	X		X							X						X						X								X	
Sacroiliac joint x-ray[j]	X																													X	
MRI[k]	X									X																				X	
BASMI & spinal mobility[l]	X		X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
BASDAI	X		X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
BASFI			X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
SF-36			X			X				X						X						X						X		X	
ASQoL			X	X	X	X				X						X						X						X		X	
MOS Sleep Scale			X			X				X						X						X						X			
EQ-5D			X			X				X						X						X						X		X	
MASES			X	X	X	X		X		X		X				X				X				X				X		X	
Total and nocturnal spinal pain			X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
Swollen and tender joint counts			X			X				X						X						X								X	
PhGADA			X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
PGADA			X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	

Table 5–1: Schedule of study assessment - Study Periods 1 to 3 (Screening until FU)

Visit #	**Scr**	**Scr day -5 to-3**	**1/BL**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9H**	**10**	**11H**	**12**	**13H**	**14**	**15H**	**16**	**17H**	**18**	**19H**	**20**	**21H**	**22**	**23H**	**24**	**25H**	**26**	**27**	**28**	**29**
Week Protocol Activity	**-6 to -1**		**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14/H**	**16**	**18/H**	**20**	**22/H**	**24**	**26/H**	**28**	**30/H**	**32**	**34/H**	**36**	**38/H**	**40**	**42/H**	**44**	**46/H**	**48**	**50**	**52/WD**	**FU[b]**
Productivity			X			X				X						X						X						X		X	
Resources utilization[m]			X			X				X						X						X						X		X	
CZP plasma concentration/ anti-CZP Abs / Biomarker			X	X	X	X				X						X						X								X	X
Genetics/epigenetics			X							X																					
Gene expression and proteomics			X			X				X																				X	
Prior and Concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IXRS	X		X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X	X	X	X
Study drug administration sc[n]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Subject training on self-injection[o]									X	X																					

Abs=antibodies; AE=adverse event; AsQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; axSpA=axial spondyloarthritis; BASMI=Bath Ankylosing Spondylitis Metrology Index; BL=Baseline;

CKD-EPI=Chronic Kidney Epidemiology Collaboration; CRP=C-reactive protein; CZP=certolizumab pegol; EQ‑5D=EuroQoL Health Status Questionnaire (5 dimensions); FU= Follow-Up; H=home; HLA-B27=Human Leukocyte Antigen-B27; IGRA=Interferon-Gamma Release Assay; IXRS=Interactive Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MOS=Medical Outcomes Study; MRI=magnetic resonance imaging; PE=physical exam; PhGADA=Physician's Global Assessment of Disease Activity; PGADA=Patient's Global Assessment of Disease Activity; sc=subcutaneously; Scr=Screening; SF‑36=Short‑Form 36‑item Health Survey; SI=sacroiliac; TB=tuberculosis; WD=Withdrawal

Note: All weeks are ±3 days compared to Baseline

[a] Informed consent: Prior to any study activities, subjects will be asked to read and sign the informed consent form for the conduct of the study. A separate informed consent form will also be obtained from subjects consenting to the use of their blood samples in a substudy for possible genetic, genomic/epigenetic, and proteomic analysis.

[b] FU: 8 weeks after Week 52/WD visit.

[c] Pulse rate, systolic and diastolic blood pressures, temperature, and respiration rate are to be measured at Screening and Baseline, thereafter pulse rate, systolic and diastolic blood pressures, temperature are to be measured at all on-site visits. If a subject experiences an AE, respiration rate will be measured in addition.

[d] Testing to rule out hepatitis B surface antigen and antibodies to hepatitis C and testing for HLA-B27 and abnormalities for estimated Glomerular Filtration Rate as measured by CKD-EPI are to be performed at Screening only.

[e] One retest of CRP is mandatory during the Screening Period within 3 to 5 days before the Baseline visit in order to meet the inclusion criteria.

[f] Pregnancy testing must be carried out for women of childbearing potential and will be serum testing at the Screening Visit and FU and urine testing (dipstick) at Baseline and Week 52/Withdrawal.

[g] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Weight is to be measured at Screening, Week 24, and at Completion at Week 52/Early Withdrawal. Height will be measured at the Baseline Visit only.

[h] Screening chest x-ray (or computed tomography of the chest) must have occurred within 3 months prior to Screening Visit and will be repeated at Week 52 or Early Withdrawal Visit only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure).

[i] TB test: IGRA test (QuantiFERON test [or Elispot test when the QuantiFERON indicated is not available]). The TB tests will be repeated at Week 52 (or at Early Withdrawal Visit if medically indicated) for subjects with previously negative TB test result. Subjects who tested positive for TB should be encouraged to complete a FU Visit (8 weeks after the Week 52/WD Visit) and follow-up information of suspected and confirmed TB cases should be provided to UCB at least after 3, 9, and 12 months of the start date of anti-TB treatment.

[j] Sacroiliac joint x-rays will be performed at Screening and WD for all subjects. An SI joint x-ray will be performed ≤12 months prior to the Baseline Visit.

[k] Magnetic resonance imaging of the spine and SI joints to be performed at Screening, Weeks 12 (SI only), 52, or Early Withdrawal Visit if MRI was performed more than 12 weeks prior to Early Withdrawal Visit.

[l] Occiput to wall distance; chest expansion; and BASMI, which includes modified Schober test, lateral spinal flexion, cervical rotation, tragus to wall distance, and maximal intermalleolar distance.

[m] Resource utilization includes: concomitant medical procedures, health care provider consultations not foreseen by the protocol, hospitalizations/emergency room visits.

[n] At on-site visit days (Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), study treatments will be administered sc at the study site by dedicated, unblinded and adequately trained site personnel. The study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. From Week 52 onwards, after completion of all on site assessments and procedures, the subject may receive further open-label treatment with CZP to be supplied to discontinued subjects or another biologics at the discretion of the Investigator.

[o] All subjects will receive training for self-injection at the study site on Weeks 10 and 12. During the training at the Weeks 10 and 12 visits, the study treatment will be self-administered under the supervision of the unblinded study personnel.

Table 5–2: Schedule of alternative study assessment with CZP - after subject discontinuation of study treatment

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

Table 5–2: Schedule of alternative study assessment with CZP - after subject discontinuation of study treatment

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

Abs=antibodies; AE=adverse event; AS=ankylosing spondylitis; AsQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CRP=C‑reactive protein; CZP=certolizumab pegol; EQ-5D=EuroQoL Health Status Questionnaire (5 dimensions); FU= Follow-Up; H=home, no site visit; IGRA=Interferon-Gamma Release Assay; IXRS=Interactive Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MOS=Medical Outcomes Study;; PE=physical exam; Q12W=every 12 weeks; sc=subcutaneously; SF‑36=Short‑Form 36‑item Health Survey; W=Week; WD=Withdrawal; wdt=withdrawal treatment

Note: If a subject switches from open-label CZP to other treatment (including biologics), the subject must follow the assessment schedule (Table 5–3) for other treatment (including biologics)

Note: All weeks are ±3 days compared to Baseline. Week 0 of the alternative schedule starts 2 weeks after the last dose of study treatment.

[a] FU: 8 weeks after Week 52/WD Visit.

[b] Pulse rate, systolic and diastolic blood pressures, temperature, and respiration rate are to be measured at wdt Week 0 thereafter pulse rate, systolic and diastolic blood pressures, temperature are to be measured at all on-site visits. If a subject experiences an AE, respiration rate will be measured in addition.

[c] Pregnancy testing must be carried out for women of childbearing potential and will be a serum test at the FU visit and a urine test (dipstick) at wdt Week 0 (prior to initiation of open-label CZP) and Week 52/Early Withdrawal Visit.

[d] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Weight is to be measured at wdt Week 0, Week 24, and at Completion at Week 52/Early Withdrawal.

[e] If the last Q12W assessment for a subject who discontinues study treatment is ≤4 weeks before the final assessments visit at Week 52, the assessment should be cancelled and the subject should instead be invited to undergo the final assessments visit at Week 52 (the Week 52 Visit is to be scheduled 52 weeks (±3 days) after Baseline).

[f] TB test: IGRA test (QuantiFERON test [or Elispot test when the QuantiFERON test is indicated but not available]). The TB tests will be repeated at Week 52 (or at Early Withdrawal Visit if medically indicated) for subjects with previously negative TB test result.

[g] Occiput to wall distance; chest expansion; and BASMI, which includes modified Schober test, lateral spinal flexion, cervical rotation, tragus to wall distance, and maximal intermalleolar distance.

[h] A separate informed consent will be obtained prior to gene expression and proteomic assessments, if applicable.

[i] Loading dose of CZP 400mg at Weeks 0, 2, and 4 must be administered by dedicated site staff.

Table 5–3: Schedule of alternative study assessment with other treatment (including biologics) - after subject discontinuation of study treatment

Visit #	1 wdt	2 wdt	3 wdt		52/WD	FU[a]
Week Protocol Activity	**0**	**12**	**24 and Q12W**	**Continue W24assessments every 12 weeks until as close as possible to W52 of the original visit schedule. Subject will then be invited to the final assessment visit at W52 ±4 weeks.[b]**	**52/WD**	**FU[a]**
Haematology/ urine/ biochemistry	X					
CRP	X	X			X	X
PE	X					X
BASDAI	X	X			X	
BASFI	X	X			X	
Total and nocturnal spinal pain	X	X			X	
Swollen and tender joint counts					X	
Patient's Global assessment	X	X			X	
Investigator's AS assessment	X	X			X	
CZP plasma concentration/ anti-CZP Abs / Biomarker	X	X				X
Prior and Concomitant medication	X	X	X		X	X
AEs	X	X	X		X	X
IXRS[c]	X	X	X		X	X
Other treatment administration	X[d]	Follow the regimen of the particular alternative treatment				

Abs=antibodies; AE=adverse event; Abs=antibodies; AE=adverse event; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; CRP=C‑reactive protein; CZP=certolizumab pegol; FU= Follow-Up; H=home, no site visit; IXRS=Interactive Response System; PE=physical exam; Q12W=every 12 weeks; W=Week; WD=Withdrawal, wdt=withdrawal treatment

Note: All weeks are ±3 days compared to Baseline. Week 0 of the alternative schedule starts 2 weeks after the last dose of study treatment.

Note: Local guidelines on initiation and monitoring of the particular treatment should be followed.

[a] FU: 8 weeks after Week 52/WD Visit.

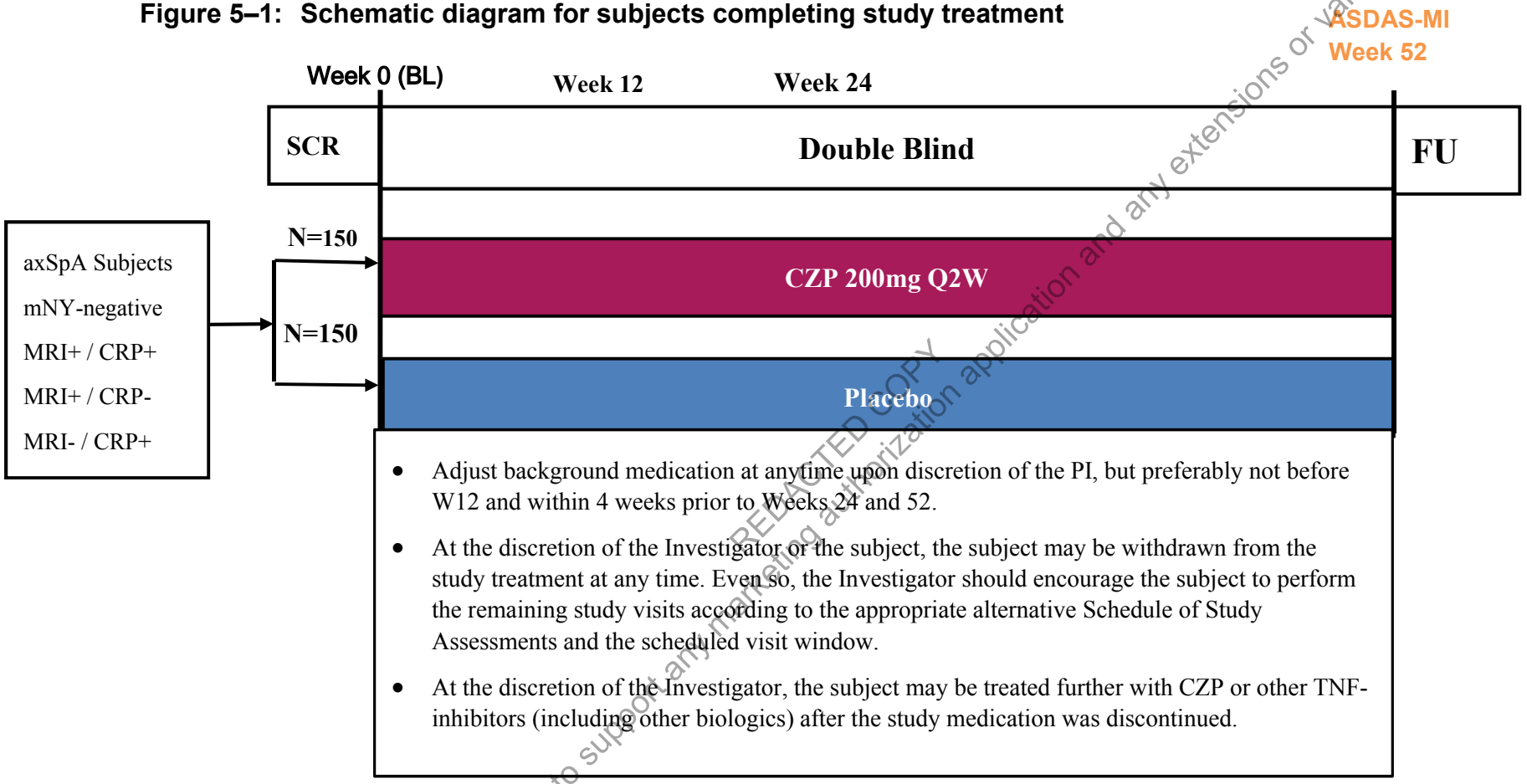
[b] If the last Q12W assessment for a subject who discontinues study treatment is ≤4 weeks before the final assessments visit at Week 52, the assessment should be cancelled and the subject should instead be invited to undergo the final assessments visit at Week 52 (the Week 52 Visit is to be scheduled 52 weeks [±3 days] after Baseline).

[c] For registration of visit only. IXRS won't assign any open treatment medication.

[d] Follow the regimen of the particular alternative treatment. Arrange for additional site visits for administration and record the treatment in the Concomitant Medication eCRF as appropriate.

5.3 Schematic diagram

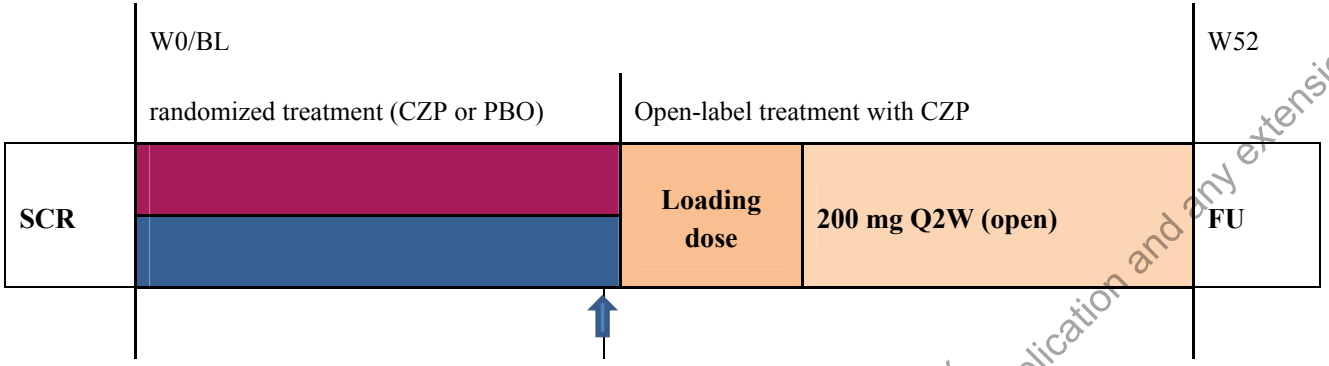
Figure 5–1: Schematic diagram for subjects completing study treatment



ASDAS-MI=Ankylosing Spondylitis Disease Activity Score major improvement; axSpA=axial spondyloarthritis; BL=Baseline; CRP=C-reactive protein; CZP=certolizumab pegol; FU=Follow-Up; mNY=modified New York criteria; MRI= magnetic resonance imaging; PI=Principal Investigator; Q2W=every 2 weeks (every other week); SCR=Screening; TNF=tumor necrosis factor-alpha inhibitor; W=week

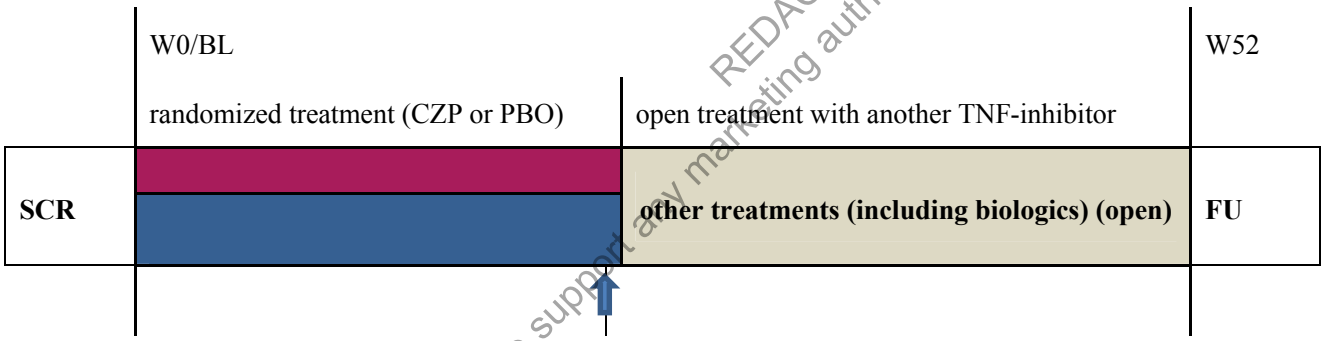
Figure 5–2: Schematic diagram for subjects discontinued from study treatment

Scenario A: The subject initiates treatment with CZP for treatment to be supplied to discontinued subjects



On discretion of the PI the study treatment is discontinued and treatment with CZP is initiated. The new treatment shall continue through to Week 52 of the regular visit schedule.

Scenario B: The subject initiates treatment with other treatments (including biologics)



On discretion of the PI the study treatment is discontinued and treatment with other treatments (including biologics) is initiated. The new treatment shall continue through to Week 52 of the regular visit schedule.

BL=Baseline; CZP=certolizumab pegol; FU=Follow-Up; PBO=placebo; PI=Principal Investigator; SCR=Screening; TNF=tumor necrosis factor-alpha inhibitor; W=week

5.4 Rationale for study design and selection of dose

The current study will evaluate nr-axSpA subjects receiving either CZP or placebo in combination with standard of care for a duration of 52 weeks. This is a unique study design to achieve an understanding of the natural history of nr-axSpA and to support the assumption that treatment with tumor necrosis factor-alpha inhibitor (TNFi) is necessary in this group of subjects. The lack of a mandatory escape arm for placebo subjects is balanced by the ability of the Investigators to modify background medications (NSAIDs, corticosteroids, analgesics, and SAARDs) during the course of the study. If the Investigator determines that a subject should be treated with other medicines (including biologics), the study medication will be discontinued and subjects will be asked to continue to come to the office for study visits to track their response to other treatments. If the Investigator choses to withdraw subjects on the other therapy, the local guidelines on initiation and monitoring of the particular treatment should be followed.

In accordance with prescribing information for CZP, 3 loading doses of 400mg Q2W should be administered upon initiation of therapy. Thus all subjects who transition to open-label CZP within the AS0006 study from the Double-Blind Period will receive this loading dose prior to the maintenance dose of 200mg Q2W. It is recognized that some subjects would have been on active CZP prior to transition to open-label CZP. However, this dosing approach is justified in all transitioning subjects as there will be no change in benefit-risk due to administration of loading dose and the blinding will be maintained in the study, preserving the data integrity.

The enrollment criteria will result in the following subgroups based on MRI and CRP:

- MRI+/CRP+
- MRI+/CRP-
- MRI-/CRP+

This 3-level MRI/CRP classification variable will be used as a stratification factor in the randomization to ensure balance across these subgroups. Taken together, these 3 subgroups encompass the nr-axSpA subject population that would benefit most from anti-TNF therapy and who have the most limited treatment options.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject or legal representative. The
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete questionnaires), visit schedule, or medication intake according to the judgment of the Investigator.
3. Subject is at least 18 years old at the Screening Visit.
4. Female subjects must be either postmenopausal for at least 1 year, surgically incapable of childbearing, or effectively practicing an acceptable method of contraception (either oral/parenteral/implantable hormonal contraceptives, intrauterine device, or barrier and

spermicide). Abstinence only is not an acceptable method. Subjects must agree to use adequate contraception during the study and for at least 10 weeks (or [for participating countries of the EU – 5 months in accordance with the Summary of Product Characteristics, SPC] longer if required by local regulations) after the last dose of study treatment. Male subjects must agree to ensure they or their female partner(s) use adequate contraception during the study and for at least 10 weeks (or [for participating countries of the EU - 5 months in accordance with the SPC] longer if required by local regulations) after their last dose of study treatment.

5. Subjects must have a documented diagnosis of adult-onset axSpA as defined by the specified ASAS criteria (not including family history and good response to NSAIDs; see Appendix 18.1) with at least 12 months symptom duration before Screening.
6. Subjects must have evidence of inflammatory back pain as defined by the ASAS criteria.
7. Subjects must NOT have sacroiliitis defined by mNY criteria (see Appendix18.2) (bilateral ≥Grade 2; unilateral ≥Grade 3) on SI x-rays (based on central reading of x-rays, within the last 12 months from Baseline).
8. Subjects must have active disease as defined by each of the following at Screening and Baseline:
   - BASDAI score ≥4
   - Spinal pain ≥4 on a 0 to 10 NRS (from BASDAI item 2)
9. Subjects must have a combination of current evidence of sacroiliitis on the screening MRI as defined by ASAS/OMERACT scoring confirmed via central reading (MRI+) and CRP either >upper limit of normal (ULN) or ≤ULN (for CRP the ULN is defined as the ULN indicative for inflammatory disease) at Baseline (CRP+ or CRP-), or no evidence of sacroiliitis on the screening MRI (MRI-) and CRP >ULN (CRP+) as follows:
   - MRI+/CRP+
   - MRI+/CRP-
   - MRI-/CRP+
10. Subjects must have had an inadequate response to, have a contraindication to, or have been intolerant to at least 2 NSAIDs. Inadequate response to an NSAID is defined as lack of response to at least 14 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID.

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

1. Subject has previously participated in this study or subject has previously been assigned to treatment in a study of the medication under investigation in this study.
2. Subject has participated in another study of an investigational medicinal product (IMP) (or a medical device) within the previous 3 months (or 5 half-lives, whichever is greater) or is currently participating in another study of an IMP (or a medical device).
3. Subject has history of chronic alcohol abuse or drug abuse within the last year.

4. Subject has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the subject's ability to participate in this study.
5. Subject has a known hypersensitivity to any components of the IMP or comparative drugs as stated in this protocol.

Axial SpA-disease-related exclusions

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

Prior medications exclusions

Subjects must not have used the following medications in the manner as detailed by the exclusion criteria in the following table (see Table 7–1).

Previous clinical studies and previous biological therapy exclusions

9. Subjects must not have received any nonbiological therapy for axSpA not listed in Table 7–1 within or outside a clinical study in the 3 months or within 5 half-lives prior to the Baseline Visit (whichever is longer).
10. Subjects must not have received any experimental biological agents (defined as those agents unlicensed for use in axSpA in Europe or the USA).
11. Subjects must not have received previous treatment with a PEGylated compound that resulted in a severe hypersensitivity reaction or an anaphylactic reaction.
12. Subjects may not have been exposed to more than 1 TNF-antagonist prior to the Baseline Visit and may not be a primary failure to any TNF-antagonist therapy (defined as no response within the first 12 weeks of treatment with the TNF-antagonist).

Medical History Exclusions

13. Female subjects who are breastfeeding, pregnant or plan to become pregnant during the study or within 3 months following the final dose of the investigational product.
14. Subjects with a history of chronic or recurrent infections (more than 3 episodes requiring antibiotics or antivirals during the preceding year), recent serious or life–threatening infection within the 6 months prior to the Baseline Visit (including hospitalization for any infection in the last 6 months or any current sign or symptom that may indicate an infection).
15. Subjects with a history of herpes zoster infection within 6 months prior to the Baseline Visit.
16. Subjects with known TB infection, at high risk of acquiring TB infection, or latent TB infection are excluded.

a. Known TB infection whether present or past is defined as:

i) Active TB infection or clinical signs and symptoms suspicious for TB (pulmonary or extra-pulmonary)

ii) History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection

iii) Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the subject's medical history.

b. High risk of acquiring TB infection is defined as:

i) Known exposure to another person with active TB infection within the 3 months prior to Screening

ii) Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high.

c. Latent TB infection (unless appropriate prophylaxis is initiated prior to study treatment and continued to completion of prophylaxis). Please refer to Section 12.6.3 for further details and instructions.

17. Subjects with concurrent acute or chronic viral hepatitis B or C or with human immunodeficiency virus (HIV) infection.
18. Subjects with history of or current active infection with Histoplasma, Coccidiodes, Paracoccidioides, Pneumocystis, nontuberculous mycobacteria (NTMB), Blastomyces, or Aspergillus.
19. Subjects must not have a history of an infected joint prosthesis at any time.
20. Subjects receiving any live (includes attenuated) vaccination within the 8 weeks prior to Baseline (eg, inactivated influenza and pneumococcal vaccines are allowed but nasal influenza vaccination is not permitted).
21. Subjects who in the Investigator's opinion have a high risk of infection (eg, subjects with leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections, and subjects who are permanently bedridden or wheelchair bound).
22. Subjects with a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.
23. Concurrent malignancy or a history of malignancy (subjects with less than 3 excised basal cell carcinomas or with cervical carcinoma in situ successfully surgically treated more than 5 years prior to Screening may be included).
24. Subjects with Class III or IV congestive heart failure as per the New York Heart Association (NYHA) 1964 criteria.
25. Subjects with a history of, or suspected, demyelinating disease of the central nervous system (eg, multiple sclerosis or optic neuritis).
26. Subjects having had major surgery (including joint surgery) within 8 weeks prior to Screening, or having planned surgery within 6 months after entering the study.

27. Subjects with a current or recent history, as determined by the Investigator, of severe, progressive, and/or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, or neurological disease.
28. Subjects with significant laboratory abnormalities, including but not limited to:
    - liver function tests >2.0 x ULN, if the subject is not treated with MTX and > ULN if subject is on concomitant MTX-treatment
    - Estimated Glomerular Filtration Rate as measured by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI; Levey et al, 2009) <60 mL/min/1.73^2
    - white blood cell ([WBC] <3.0x10^9/L).
29. Subjects with any other condition which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study.

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care.

Subjects should be withdrawn from the study if any of the following events occur:

1. Subject develops an illness that would interfere with his/her continued participation.
2. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. Subject withdraws his/her consent.
4. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
5. The Sponsor or a regulatory agency requests withdrawal of the subject.
6. Subject's subsequent TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). Refer to Section 12.6.3 for further details and instructions.

Subjects should be withdrawn from the study-treatment if,

7. The Investigator decides to initiate an alternative treatment due to an unsatisfactory response to the study treatment, or
8. Subjects take any of the prohibited medications in Table 7–1 and Section 7.8.2

If a subject is withdrawn from study treatment, the Investigator should encourage the subject to continue participation in the study in accordance with the appropriate alternative schedule of study assessments (Table 5–2 or Table 5–3). The treatment that the subject receives following withdrawal of study medication is at the discretion of the Investigator. Open-label CZP for treatment to be supplied to discontinued subjects will be made available as a treatment option according to the local requirement mandated in the region. UCB will provide this medication free of charge. Alternatively, the Investigator may treat the subject with other treatments (including biologics) as deemed appropriate by local regulations. If the Investigator choses to

withdraw subjects on the other therapy, the local guidelines on initiation and monitoring of the particular treatment should be followed.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject from the double-blind study treatment in advance. The reason for discontinuation of the double-blind study treatment must be recorded in the CRF as appropriate.

Although the subject may be withdrawn from the double-blind study treatment at any time, every effort should be made to retain the subject in the study and encourage compliance of the subject with the scheduled study visits. For subjects who fail to return to study visit(s) or are considered lost to follow up, the Investigator should specifically communicate (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents). In case the attempts to direct contact the subject fail, the Investigator is encouraged to gain information about the wellbeing of the subject at the end of the regular visit schedule (Week 52) from other sources in compliance with local regulations. All results of observations and communication with the subject, including and not limited to the relevant information on his/her wellbeing, must be recorded in the source documents.

If a subject is withdrawn from the study, the narrative description of the reason(s) for removing the subject must be recorded in the source documents. The CRF must document the primary reason for withdrawal.

Subjects withdrawn from the study will not be replaced.

7 STUDY TREATMENTS(S)

7.1 Description of investigational medicinal product(s)

The IMP will be supplied under the responsibility of the UCB Clinical Supply Unit. The frequency at which IMP will be supplied to each individual center will be adapted to the recruitment capacity of that center and to the expiry date of the IMP and will be managed by the interactive response system (IXRS).

Drug supplies will consist of the following:

Certolizumab pegol is supplied as a sterile, clear, colorless to slightly yellow liquid solution with a pH of approximately 4.7 in 1mL single use glass prefilled syringe (PFS) with a 25G ½ inch thin wall needle for sc injection. Each syringe contains an extractable volume of 1mL at a concentration of 200mg/mL of CZP in 10mM sodium acetate buffer and 125mM sodium chloride as a tonicity agent.

Placebo is supplied in a PFS with a 25G ½ inch thin wall needle, containing an injectable volume of 1mL 0.9% saline for single use.

Due to the difference in presentation and viscosity between CZP and placebo, special precautions will be taken in order to ensure maintained blinding of the study (unblinded/blinded site personnel and monitors).

7.2 Treatment(s) to be administered

Treatments to be administered are as described in Section 5.1.

7.2.1 Treatment administration

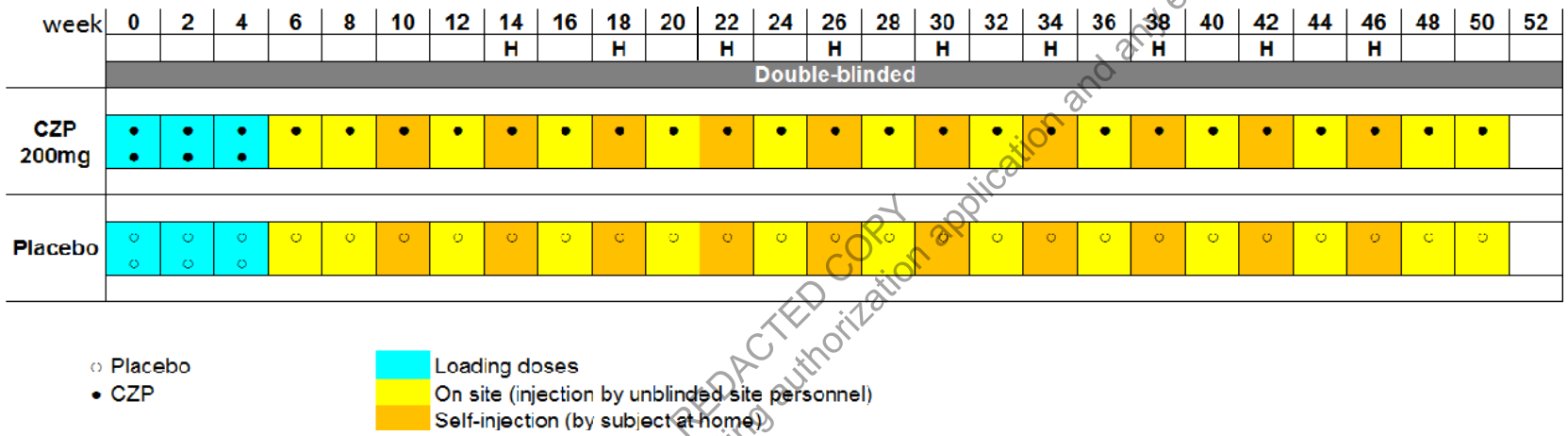
A pharmacy manual will be provided to each site containing instructions regarding drug preparation and dosing. The injection schedule is described in Section 7.2.2.

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), study treatments will be administered sc at the study site by dedicated, unblinded and adequately trained site personnel. The study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. All subjects will receive training for self-injection at the study site on Weeks 10 and 12. During the training on Weeks 10 and 12 visits, the study treatment will be self-administered under the supervision of the unblinded study personnel.

Injections should be administered with a minimum of 10 days between the CZP 200mg Q2W injections.

7.2.2 Study AS0006 injection schedule

Figure 7–1: Injection schedule



CZP=Certolizumab pegol; H=home

7.3 Packaging

Certolizumab pegol and placebo are packaged and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. They are suitably packaged in such a way as to protect the IMPs from deterioration during transport and storage.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language. Details on Labeling will be provided in the Pharmacy manual.

7.5 Handling and storage requirements

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. The IMP stored by the Investigator is to be kept in a secured area with limited access. The IMP containers should be stored at 2 to 8°C and protected from light. Additional information regarding the receipt of the drug and return handling will be specified in the Pharmacy Manual.

Appropriate storage conditions must be ensured by a controlled temperature and by completing a temperature log in accordance with local requirements but at least once per working day with minimum and maximum temperatures reached over the time interval.

In case an out of range temperature is noted, it must be immediately communicated to the Sponsor' designee in accordance with the Pharmacy Manual.

The Investigator (or designee) will instruct the subject to store the IMP following the instructions on the label.

Detailed information on handling and storage of IMP will be given in the Pharmacy Manual.

7.6 Drug accountability

A drug accountability form will be used to record IMP dispensing and return information during the course of the study. Details of any drug lost (due to breakage or wastage), not used, disposed of at the study site, or returned must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) and unused IMP containers must be reconciled and returned to UCB (or designee), preferably in their original packaging. Instructions on how to use and store the IMP will be provided. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the IMP is used only in accordance with the protocol.

All study drug documentation (eg, shipping receipts, drug accountability logs, IXRS randomization materials) must be maintained and accessed by unblinded, trained site personnel only. Designated, unblinded site personnel must be appropriately trained and licensed (per country guidelines) to administer injections. Each site will be required to have a written blinding plan in place signed by the Principal Investigator, which will detail the site's steps for ensuring that the double-blind nature of the study is maintained from Week 0 to Week 52.

7.7 Procedures for monitoring subject compliance

Drug accountability must be recorded on the drug accountability form.

If a subject is found to be persistently noncompliant (missing 3 or more doses over any period of 52 weeks), the subject will be withdrawn from the study. A subject will be withdrawn from the study if 3 consecutive doses were missed prior to the primary endpoint assessment. No missing doses are allowed in the first 12 weeks of the study. Doses of IMP that were missed due to a reasonable interfering AE that does not allow administration of an anti-TNF due to safety reasons will not be considered for the evaluation of subject compliance. Evaluation of the reasonability of the AE must be discussed immediately with the Medical Monitor.

7.8 Concomitant medication(s)/treatment(s)

For any subject taking any medication, including over the counter products, nutraceuticals, or herbal medications at Screening or at any time during the course of the study, an accurate record must be kept in the clinic chart (source documentation) and the CRF. This record should include the name of the drug, the dose, the date(s) of administration, and the indication for use.

Changes in the concomitant medication to treat the burden of the predominantly existing disease of the nr-axSpA symptoms is allowed during the placebo-controlled period of the study under the conditions listed below. A change in the first 12 weeks of the study should be avoided.

Table 7–1: Concomitant Medications (prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
Analgesics (including, but not limited to acetaminophen, paracetamol, opiates, or combinations thereof)	Up to maximum approved dose	Any change in stable dose regimen is excluded in the 14 days prior to the Baseline Visit.	Any ad hoc (prn) use of analgesics is not permitted within 24 hours prior to any post-Screening visit. An increase or addition in opiates or a combination with opiates is not recommended between Week 0 and Week 12 or within 4 weeks prior to the Week 24 or Week 52 visits.

Table 7–1: Concomitant Medications (prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
NSAIDs (including COX 2 inhibitors)	Up to maximum approved dose regimen	Any change in stable dose regimen is excluded in the 14 days prior to the Baseline Visit.	Any ad hoc (prn) use of NSAIDs is not permitted within 24 hours prior to any post-Screening visit. Changes in NSAID doses should be avoided between Week 0 and Week 12 or within 4 weeks prior to the Week 24 or Week 52 visits.
Oral corticosteroids	Maximum allowed ≤10mg daily total prednisone equivalent[a]	Any change in stable dose used for axSpA in the 28 days prior to the Baseline Visit. If a taper of oral corticosteroids is planned this should be completed 14 days prior to Baseline visit.	Maximum allowed ≤10mg daily total prednisone equivalent[a] Changes in dose or initiation of corticosteroids (including tapers) should be avoided between Week 0 and Week 12 or within 4 weeks prior to the Week 24 or Week 52 visits.
Corticosteroids (im)	Any dose	Use in the 28 days prior to the Baseline Visit.	Corticosteroids (im) must not be used during the study.
Corticosteroids (ia)	Up to maximum approved dose	Use in the 28 days prior to the Baseline Visit.	SIJ corticosteroid (ia) injections are not allowed during the study. Peripheral joint injections are permitted.

Table 7–1: Concomitant Medications (prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
Corticosteroids (iv)	Up to maximum approved dose	Use in the 28 days prior to the Baseline Visit.	Doses of corticosteroids (iv) may be used during the study for acute illnesses as long as the dose is not given within 1 week prior to Week 12, Week 24, or Week 52 and the underlying disease does not present a contraindication to the subject remaining in the study. Indications might include dermatitis, gastroenteritis, asthma exacerbation, and pneumonia.
Hyaluronic acid (ia)	Any dose	Use in the 28 days prior to the Baseline Visit.	Used in knee as needed after Week 12 Visit.
SAARDs[b]: SSZ and/or HCQ and/or MTX and/or LFN and/or AZA	Maximum allowed: SSZ ≤3g daily HCQ ≤400mg daily MTX ≤25mg weekly AZA ≤150mg/day LFN ≤20mg/day (see exclusion criteria for washout requirements)	SAARD initiated and or any change in the dose regimen in the 28 days prior to the Baseline Visit. Use of LFN in the 6 months prior to the Baseline Visit unless a cholestyramine washout has been performed. In case of a cholestyramine washout, use 28 days prior to the Baseline Visit is acceptable.	Changes in SAARD doses should not be made between Week 0 and Week 12 or within 4 weeks prior to Week 24 or Week 52 visit. SAARD dose reduction to manage intolerance or safety issues is allowed at any time during the study at the Investigator's discretion.
SAARDs: AZA, cyclosporine, cyclophosphamide, mycophenolic acid, apremilast	Up to maximum approved dose	Use within 28 days prior to the Baseline Visit	Changes in SAARD doses or initiation of a new SAARD should be avoided between Week 0 and Week 12 or within 4 weeks prior to Week 24 or Week 52 visit

Table 7–1: Concomitant Medications (prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
Anti-TNF therapies IFX ADA ETN GOL CZP	Any dose	For IFX, ADA, and GOL, any use within the 3 months prior to the Baseline Visit. For CZP any exposure history. For ETN, use within the 28 days prior to the Baseline Visit. Only 1 previous biologic is allowed.	If biologic therapy is required the subject must be discontinued from study medication and should conduct the remaining visits according to Figure 5–2.
Other rheumatologic therapies: abatacept rituximab anti-IL17 tocilizumab ustekinumab tofacitinib biosimilars to any approved biologic	Any dose	Any exposure history.	If other rheumatologic therapies are required the subject should be discontinued from study medication and should conduct the remaining visits according to Figure 5–2.
Osteoperosis Medications: eg, risedronate alendronate ibandronate denosumab cathepsin K inhibitor cinacalcet calcitonin	Up to maximum approved dose	All stable osteoporosis medications are permitted except for bisphosphonates (iv).	If the treatment is initiated during the study, the subject should be discontinued from study medication and should conduct the remaining visits according to Figure 5–2. Osteoporosis medications with the exception of bisphosphonates (iv) are allowed without restriction. Bisphosphonates (iv) are not permitted any time within the study.

Table 7–1: Concomitant Medications (prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
Intravenous Bisphophonates: zoledronic acid ibandronate pamidronate	Any dose	Zoledronic acid: any use within the 3 years prior to randomization Ibandronate or pamidronate: any use within the past 2 years.	If iv bisphosphonate treatment is initiated during the study, the subject should be discontinued from study medication and should conduct the remaining visits according to Figure 5–2.

ADA=adalimumab; axSpA=axial spondyloarthritis; AZA=azathioprine; COX 2=cyclooxygenase 2; CZP=certolizumab pegol; DMARD=disease-modifying antirheumatic drug; ETN=etanercept; GOL=golimumab; HCQ=hydroxychloroquine; IFX=infliximab; ia=intra-articular; IL=interleukin; im=intramuscular; iv=intravenous; LFN=leflunomide; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; RA=rheumatoid arthritis; SAARD=slow-acting antirheumatic drug; SIJ= sacroiliac joint injection; SSZ=sulfasalazine; TNF=tumor necrosis factor

[a] A table of corticosteroid equivalent doses can been found in Appendix 18.3.

[b] Throughout the text, we refer to compounds such as SSZ and MTX as SAARDs. These medications are also commonly referred to as DMARDs, but since there is no evidence that they are in fact disease-modifying in axSpA (unlike in RA), we have opted for the more appropriate SAARD terminology.

7.8.1 Permitted concomitant treatments for axSpA (medications and therapies)

The Investigator must make decisions regarding changes in background medications based upon the subject's response to previous therapy, medical history and the physician's judgment as to how to manage the axSpA disease symptoms. If possible, the following treatment recommendations for modifying background medications should be considered:

- NSAIDs including cyclooxygenase-2 (COX-2) inhibitors: ad hoc as needed (prn) should not be used 24 hours of any post-Screening study visit. As subjects should be on stable dose of background medication at study entry, a change in the first 12 weeks of the study should be avoided. Changes in dose and type of NSAID should not be made within 4 weeks prior to Week 24 and 52 visits.
- Modify the SAARD if needed to treat peripheral symptoms.
- Specific SAARDs only (SSZ and/or HCQ and/or MTX): maximum SSZ ≤3g daily; HCQ ≤400mg daily; MTX ≤25mg weekly allowed. As subjects should be on stable dose of background medication at study entry, a change in the first 12 weeks of the study should be avoided. Changes in SAARDs doses should not be made within 4 weeks before Week 24, or Week 52 visit.
- Stable doses of analgesics (including, but not limited to acetaminophen, paracetamol, NSAIDs, opiates, or combinations thereof) will be permitted except that ad hoc prn usage is prohibited within 14 days of Baseline and no ad hoc use prior to any Post-Screening visit. As

subjects should be on stable dose of background medication at study entry, a change in the first 12 weeks of the study should be avoided. An initiation of a new chronic opiate or a combination with opiates is not recommended between Week 0 and Week 12 or within weeks 4 of the Week 24 or Week 52 visits.

- Add or modify the corticosteroids (see Section 7.8.2 for prohibited corticosteroids):
  - Oral (maximum allowed daily total prednisone equivalent dose of ≤10mg). Oral corticosteroid tapers of 14 days prior to Baseline are allowed as long the maximum daily dose is ≤10mg. Changes in dose or initiation of corticosteroids (including tapers) should be avoided between Week 0 and Week 12 or within 4 weeks prior to Week 24 or Week 52 visits.
  - Corticosteroids administered intravenously (iv) will be permitted for the purposes of stress dosing for a surgical procedure under general or spinal anesthesia. Further they may be used during the study for acute illnesses as long as the dose is not given within a week of an assessment (Week 12, 24 or 52) and the underlying disease does not present a contraindication to the subject remaining in the trial. Indications might include dermatitis, gastroenteritis, asthma exacerbation, and pneumonia.
- Other treatments (including biologics): If the subject requires the start of other treatments (including biologics) at the discretion of the Investigator, the subject must be withdrawn from the blinded study medication. Every effort should be made to retain the subject in the study and encourage attendance of future study visits.
- The Investigator should refrain from making major changes in background medication between Week 0 and Week 12, as much as possible. Major changes in background medications within 4 weeks of Week 24 or Week 52 should be avoided.

Depending on the subject's response to previous therapy, the Investigator may also reduce the assigned background medication. This change should not be made between Week 0 and Week 12. Major changes in background medications should be avoided within 4 weeks prior to Week 24, or Week 52.

If the Investigator discontinues the double-blind study treatment and initiates therapy with CZP, UCB will supply the subject with the CZP. UCB is offering CZP in accordance with the local regulatory requirements for a maximum duration of 2 years or until marketing authorization is granted for CZP (if applicable), whichever comes first. If the decision is made to start a different treatment (including biologics), UCB will not be supplying the medication.

7.8.2 Prohibited concomitant and rescue treatments (medications and therapies)

Prior medication exclusions and washout periods are listed in Section 6.2. In addition, use of the following concomitant medications is prohibited during the study, except where indicated:

- Corticosteroids (administered iv/ intra-articular [ia]) are permitted only as described in Section 7.8.1. Intramuscular and sacroliliac injection (SIJ) ia corticosteroids are not permitted.
- Hyaluronic acid is permitted for the use in the knee after Week 12.

- Biologicals (TNF-antagonists: IFX, ADA, ETN, GOL, abatacept (ABA), commercially available CZP), anti-CD20, tocilizumab, ustekimumab, also any other biological response modifiers are excluded.
- All iv bisphosphonates are excluded.

If the subject requires any of the medications specified in this section, the subject must be discontinued from the study-treatment prior to the initiation of these medications. Before starting these therapies the Investigator should contact the Study Physician.

If the subject is discontinued from study-treatment in order to initiate other treatments (including biologics), the subject will be encouraged to return to the site for future study visits to continue to collect data important for study integrity.

If the subject initiates therapy with CZP, UCB will supply the subject with CZP. If the decision is made to start a different therapy, UCB will not be able to supply such medication.

Subjects must not participate in any other clinical study for any indication or receive any unauthorized medication during the study period.

The administration of live vaccines is not recommended for subjects treated with TNF antagonists. Live vaccines should not be administered 8 weeks prior to Baseline. If immunization with a live organism based vaccine is considered during the study, the clinician is urged to carefully weigh the risks vs benefits of immunization. If the subject is going to proceed with live organism based immunization, the subject must be withdrawn from the study prior to administration of the vaccine. Such vaccines must be recorded in the respective section of concomitant module of the CRF.

7.9 Blinding

Due to differences in presentation and viscosity between CZP and placebo, special precautions will be taken in order to ensure blinding of the study. The subject will receive the IMP throughout the study duration for each single administration in a sealed box with PFS containing either CZP 200mg or placebo. Packaging and labeling will be done in a way to ensure that the provided box including the PFS will not provide any information about the assigned treatment (CZP 200mg or placebo). Administration of the IMP will be done according to the schedule of study assessments (Table 5–1) either on-site by appropriately trained unblinded study personnel or at home by the subject him/herself. Pharmacokinetic and antibody data will be provided only after the study is unblinded.

7.9.1 Maintenance of study treatment blind

All subject treatment details will be allocated and maintained by the IXRS.

The study will be double-blind and placebo controlled for 52 weeks. No study team member involved in the clinical conduct will have access to the randomization schedule until after database lock and unblinding.

If the Investigator decides to discontinue the study treatment and initiate open-label treatment with CZP or other treatment (including biologics), efforts will be made to ensure that the blinding of the previously assigned study treatment will be maintained. This is to ensure that in case open-label treatment with CZP is chosen by the Investigator, the 3 loading doses of CZP

400mg Q2W will be administered by dedicated study personnel without disclosing to the subject the use of the PFS. After the last loading dose the subject can self administer CZP until Week 52 of the regular visit schedule.

7.9.2 Breaking the treatment blind in an emergency situation

All Sponsor, Investigator site, and Contract Research Organization (CRO) staff involved with the study will be blinded to the treatment code until the database lock ie, after completion of the Double-Blind Period with the following exceptions:

- Sponsor clinical study supplies coordinator, packager, and qualified person
- Pharmacy monitors that monitor unblinded pharmacy documentation
- Sponsor pharmacovigilance staff reporting serious adverse events (SAEs) to regulatory authorities
- Laboratory staff analyzing blood samples for CZP plasma concentrations and anti-CZP antibodies
- Site study drug administrator

The appropriate persons (Investigators, Single Safety Case Management [SSCM] - Safety Officer, Medical Monitor) will be provided with an individual password to access the IXRS menu that will enable them to unblind a subject's double-blind treatment allocation. This password must be kept confidential and not shared with any other persons. The IXRS will be able to identify the individual who has unblinded a subject's treatment allocation. The IXRS will be accessible at all times. If possible, Investigators are advised to contact the company or its representatives prior to unblinding the treatment allocation of subjects.

Under normal circumstances, the blinded treatment must not be revealed. In the case of a medical emergency, UCB or its representatives preferably should be contacted prior to any unblinding. The blind should be broken only if doing so will change the decision-making as to the subject's treatment or clinical intervention. Any unblinding performed by the Investigator of the IMP must be documented and explained by the Investigator. If the blind is broken, the date, the reason for the breaking the blind, and person doing so must be recorded. UCB or its representatives must be notified immediately if the blind is broken.

In the event of an emergency, it will be possible to determine which treatment arm and dose the subject had been allocated to by calling the IXRS. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor (or equivalent) should be consulted prior to unblinding, whenever possible.

For the product and study information and emergency unblinding purposes, the Sponsor will provide each Investigator with an appropriate quantity of clinical study subject cards. Each subject will be instructed to keep the card with him/her at all times. These subject cards will be written in the language of the subject. The Investigator will fill in each card with the details of his/her contact information (eg, Investigator stamp) and subject identifier. The card will be distributed to the subject at the time of informed consent.

The Clinical Project Manager (CPM) will be informed immediately via the IXRS when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the IMP

performed by the Investigator must be recorded in the source documents and on the Study Termination CRF page.

7.10 Randomization and numbering of subjects

7.10.1 Interactive Response System

An IXRS is used for subject registration as well as randomization and treatment administration.

To enroll a subject, the Investigator must contact the IXRS and provide brief details of the subject to be enrolled. Each subject will be assigned a unique subject number. Enrolled subjects who withdraw from the study prior to randomization will retain their subject number without receiving a randomization number (ie, subject numbers will not be reassigned).

The IXRS will allocate kits of study medication at Week 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50.

7.10.2 Randomization

Randomization will be stratified on:

- Region
- MRI/CRP classification

Subjects will be classified as MRI+/- depending on whether or not they have evidence of sacroiliitis on MRI at Screening based on the ASAS/OMERACT definition. Subjects will be classified as CRP+/- based on the CRP value obtained at the second Screening visit scheduled to occur 3 to 5 days prior to Baseline. Subjects will be categorized as CRP+ if their CRP value is above the level indicative of inflammatory disease at this visit. Otherwise, they will be considered CRP-. Based on these definitions, the stratification for MRI/CRP classification will have the following 3 levels:

- MRI+/CRP+
- MRI+/CRP-
- MRI-/CRP+

The IXRS will be designed to ensure that at least 20% and no more than 40% of the randomized subjects belong to 1 of the 3 clinical subgroups above.

To randomize a subject, the Investigator must contact the IXRS and provide brief details of the subject that is to be randomized. The IXRS will automatically inform the Investigator of the subject's randomization number. Each subject will be assigned a unique randomization number. This randomization number will be required in all communications between the Investigator (or his/her designee) and the IXRS regarding a particular subject. The IXRS will allocate kit numbers to the subjects based on the randomization list over the course of the study. Randomization numbers and kit numbers will be tracked via the IXRS and also will be required to be entered into the CRF.

Randomization schedules will be generated prior to start of the study. Subjects will be allocated to treatment in a 1:1 ratio (CZP 200mg: placebo).

8 STUDY PROCEDURES BY VISIT

Section 5.2 (Schedule of study assessments) provides a general overview of study assessments. A detailed listing of procedures to be undertaken at each visit is described below.

During the study the Investigator will assess the subjects over the entire study period of approximately 66 weeks including a FU Period of 8 weeks after the final Week 52/WD Visit. Visit windows of ±3 days on either side of the scheduled visit are permitted; however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±3 days is relative to Baseline and is applicable for all subsequent visits. Changes to the dosing schedule outside of the 3 day window must be discussed with the Medical Monitor and may result in subject withdrawal. Assessments required at each visit are detailed below.

8.1 Screening Visit (-6 to -1 days)

Prior to any study activities, subjects will be asked to read and sign an informed consent form that has been approved by an IEC/IRB and the Sponsor and which complies with regulatory requirements. Subjects will be given adequate time to consider any information concerning the study given to them by the Investigator or designee. As part of the informed consent process, subjects will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study.

Assessments at the Screening Visit include:

- Confirm inclusion/exclusion criteria
- Confirm informed consent
- Demographic data (includes date of birth, gender, race/ethnicity)
- Significant past medical and procedure history and concomitant disease (includes allergy and any current symptoms) including axSpA history
- Vital signs (pulse rate, systolic and diastolic blood pressure, temperature, and respiratory rate)
- Hematology, biochemistry, and urine for clinical laboratory values (includes a serum pregnancy test for women of childbearing potential and testing to rule out hepatitis B surface antigen and antibodies to hepatitis C, CRP, and HLA-B27)
- Physical examination (including weight)
- Chest x-ray (must occur within 3 months prior to Screening Visit)
- TB test: IGRA test (QuantiFERON test [or Elispot test when the QuantiFERON test is indicated but not available])
- TB evaluation questionnaire
- SI joint x-ray (centrally read). An SI joint x-ray performed ≤12 months prior to the Baseline Visit maybe used as the Baseline assessment provided that the film can be submitted and meets the requirements for central reading
- MRI (spine and SI joints, centrally read)

- BASMI and spinal mobility assessments
- BASDAI
- Prior and concomitant medication
- Contact the IXRS to indicate the subject has been screened

The period between the Screening and Baseline Visits should not exceed 6 weeks. The Screening chest x-ray should be read by a radiologist/pulmonologist and must exclude evidence of TB. The qualifying CRP levels from the Screening Visit will be used for the inclusion criteria review at Baseline.

One retest of CRP is mandatory during the Screening Period within 3 to 5 days before the Baseline visit in order to meet the inclusion criteria.

One rescreening of subjects with latent TB who are able to complete a minimum of 4 weeks of TB therapy within the Screening Period is permitted. In this event, all Screening assessments must be repeated.

8.2 Baseline Visit (Week 0)

Subjects agreeing to participate in the study, after giving signed informed consent, will have the following procedures performed/recorded prior to study drug administration:

- Review of inclusion/exclusion criteria. Note: The qualifying CRP levels from the Screening Period 3 to 5 days before Baseline will be used for the inclusion criteria review and for randomization stratification. The result of the centrally read MRI and X-ray must be available for the inclusion criteria review
- Vital signs (pulse rate, systolic and diastolic blood pressure, temperature, and respiration rate)
- Blood samples will be collected for hematology and biochemistry analyses
- Urine will be collected for urinalysis and for a urine pregnancy test for women of childbearing potential
- Physical examination (including height and extra-articular assessments)
- TB questionnaire
- BASMI and spinal mobility
- BASDAI
- BASFI
- SF-36
- ASQoL
- MOS Sleep Scale
- EQ-5D
- MASES

- Total spinal pain NRS and nocturnal spinal pain NRS
- Swollen and tender joint counts
- PGADA
- PhGADA
- Productivity measures (WPS)
- Resources utilization
- Plasma for CZP concentration, anti-CZP antibodies, and biomarkers
- Genetics/epigenetics, if applicable
- Gene expression and proteomics, if applicable
- Concomitant medication
- AEs
- Contact IXRS to randomize subject and to obtain kit number
- Study drug administration (after all other visit assessments are completed and laboratory samples are drawn)

8.3 Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, and 50 (all visits ±3 Days relative to Baseline)

Assessments at these visits include:

- Vital signs; pulse rate, systolic and diastolic blood pressures and temperature (respiration rate will be assessed in addition if the subject experiences an AE) (at all on-site visits except Week 1)
- Blood samples will be collected for hematology, biochemistry, and CRP (Weeks 2, 4, 8, 12, 24, 36 only)
- CRP for the calculation of ASDAS (Weeks 16, 20, 28, 32, 40, 44, and 48)
- Urine will be collected for urinalysis (Weeks 2, 4, 8, 12, 24, and 36 only)
- Physical examination (Weeks 2, 4, 8, 12, 16, 24, and 36), including weight at Week 24 and at Completion at Week 52/Withdrawal
- Extra-articular assessments (Weeks 4, 12, 24, 36, and 48 only)
- TB questionnaire (Weeks 12, 24, and 36 only)
- MRI (SI joints only, Week 12 only)
- BASMI and spinal mobility (at all on-site visits except Weeks 6, 10, and 50)
- BASDAI (Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 only)
- BASFI (Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 only)

- SF-36 (Weeks 4, 12, 24, 36, and 48 only)
- ASQoL (Weeks 1, 2, 4, 12, 24, 36, and 48 only)
- MOS Sleep Scale (Weeks 4, 12, 24, 36, and 48 only)
- EQ-5D (Weeks 4, 12, 24, 36, and 48 only)
- MASES (Weeks 1, 2, 4, 8, 12, 16, 24, 32, 40, and 48 only)
- Total spinal pain NRS and nocturnal spinal pain NRS (Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 only)
- Swollen and tender joint counts (Weeks 4, 12, 24, and 36 only)
- PhGADA (Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 only)
- PGADA (Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 only)
- Productivity measures (WPS) (Weeks 4, 12, 24, 36, and 48 only)
- Resource utilization (Weeks 4, 12, 24, 36, and 48 only)
- Plasma for CZP concentration, anti-CZP antibodies, and biomarkers (Weeks 1, 2, 4, 12, 24, and 36 only)
- Genetics and epigenetics (Week 12 only), if applicable
- Gene expression and proteomics (Weeks 4 and 12), if applicable
- Concomitant medication
- AEs
- Contact IXRS to obtain next kit number (Week 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50)
- Study drug administration (after all other visit assessments are completed and laboratory samples are drawn) (all visits except Week 1)
- Subject training on self-injection (Weeks 10 and 12)

8.4 Every 4 weeks (± 3 days) during home injection period from Week 14 to Week 46 (Week 14, 18, 22, 26, 30, 34, 38, 42, and 46)

The following assessments are to be performed by telephone:

- Concomitant medication
- AEs

8.5 Completion Visit (Week 52)/Early Withdrawal (±3 days)

Assessments at this visit include:

- Vital signs; pulse rate, systolic and diastolic blood pressure, and temperature (respiration rate will be assessed in addition if the subject experiences an AE)
- Blood samples will be collected for hematology, biochemistry, and CRP

- Urine will be collected for urinalysis and for a urine pregnancy test for women of childbearing potential
- Physical examination (including weight)
- Extra-articular assessments
- Chest x-ray only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection
- TB test: IGRA test (QuantiFERON test [or Elispot test when QuantiFERON test is indicated but not available]) only for subjects who have not had a previously positive TB test result
- TB Questionnaire
- Sacroiliac joint x-ray
- MRI for spine and SI joints (at Early Withdrawal Visit if previous MRI was performed more than 12 weeks prior to Early Withdrawal Visit)
- BASMI and spinal mobility
- BASDAI
- BASFI
- SF-36
- ASQoL
- EQ-5D
- MASES
- Total spinal pain NRS and nocturnal spinal pain NRS
- Swollen and tender joint counts
- PhGADA
- PGADA
- Productivity measures (WPS)
- Resources utilization
- Plasma for CZP concentration, anti-CZP antibodies, and biomarkers
- Gene expression and proteomics, if applicable
- Concomitant medication
- AEs
- Contact IXRS to indicate that subject has completed or withdrawn from the study

8.6 FU Visit (8 weeks after the Week 52/WD visit)

Assessments at this visit include:

- Vital signs; pulse rate, systolic and diastolic blood pressure, and temperature (respiration rate will be assessed in addition if the subject experiences an AE)
- Blood samples will be collected for hematology, biochemistry, CRP, and serum pregnancy test for women of childbearing potential
- Urine will be collected for urinalysis
- Physical examination
- Plasma for CZP concentration, anti CZP antibodies, and biomarkers
- Concomitant medication
- AEs
- Contact IXRS to indicate that subject has completed FU

8.7 Unscheduled Visits

It is at the Investigator's discretion to initiate an Unscheduled Visit, if deemed necessary by the Investigator for the subject's safety and well-being. At this visit, any of the following or other assessments at the Investigator's discretion may be performed depending on the reason for the visit:

- Vital signs
- Blood samples for hematology, biochemistry, other testing such as for TB or CRP
- Urine for urinalysis and/or pregnancy testing (for women of childbearing potential)
- Physical examination
- Concomitant medication
- AEs
- TB questionnaire
- Contact IXRS to indicate that subject attended an unscheduled visit

8.8 Alternative Visit schedules after subject discontinuation of study treatment

Alternative schedules for assessment for subjects who discontinue the study treatment are described in this section. Assessments are to be continued as at Week 24 every 12 weeks until as close as possible to Week 52 (within ±3 days of the originally planned Week 52 visit) of the original visit schedule. Subject will then be invited to the final assessment visit at Week 52.

The following assessments will be performed for subjects who are treated with open-label CZP after discontinuation of study treatment:

- Vital signs; pulse rate, systolic and diastolic blood pressure, and temperature (respiration rate will be assessed in addition if the subject experiences an AE) at withdrawal treatment (wdt)

Weeks 0, 2, 4, 12, 24 (and every 12 weeks [Q12W]), 52, and FU (8 weeks after Week 52 Visit)

- Blood samples will be collected for hematology, biochemistry analyses, urine will be collected for urinalysis at wdt Weeks 0, 12, 24 (and Q12W), 52 and FU and CRP at Week 0, 12, 24 (and Q12W), 52, and FU (8 weeks after Week 52 Visit)
- Pregnancy test for women of childbearing potential at wdt Weeks 0, 52 and FU (serum testing)
- Physical examination at wdt Weeks 0, 4, 12, 24 (and Q12W), 52, and FU
- Extraarticular assessments at wdt Weeks 12, 24 (and Q12W), and 52
- TB test at wdt Week 52 only
- TB questionnaire at wdt Weeks 0, 12, 24 (and Q12W), and 52
- SF-36, AsQoL, MOS Sleep Scale, EQ-5D, MASES at wdt Weeks 0, 12, 24 (and Q12W), and 52
- BASMI & spinal mobility, BASFI, Total and nocturnal spinal pain, swollen and tender joint counts, BASDI, Patient's Global assessment, and Investigator's AS assessment at wdt Weeks 0, 4, 12, 24 (and Q12W), and 52
- Plasma for CZP concentration, anti CZP antibodies, and for biomarkers at wdt Weeks 0, 4, 12, 24 (and Q12W), 52 and FU
- Gene expression and proteomics at wdt Week 52 only
- Concomitant medication at wdt Weeks 0, 2, 4, 12, 24 (and Q12W), 52, and FU
- AEs at wdt Weeks 0, 2, 4, 12, 24 (and Q12W), 52, and FU
- IXRS (for treatment assignment) at wdt Weeks 0, 2, 4, 12, 24 (and Q12W), 52, and FU
- CZP administration at wdt Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 (and Q12W), 52, and FU. Loading dose of CZP 400mg at Weeks 0, 2 and 4 must be administered by dedicated site-staff

The following assessments will be applied for subjects who receive an alternative study assessment with other treatment (including biologics) after discontinuation of study treatment:

- Blood samples will be collected for hematology, biochemistry, and urine will be collected for urinalysis at wdt Week 0, CRP analyses will be performed at wdt Weeks 0, 12, 52, and FU
- Physical examination at wdt Week 0 and FU.
- BASDAI, BASFI , total and nocturnal spinal pain, Patient's Global assessment, and Investigator's AS assessment at wdt Weeks 0, 12, and 52
- Swollen and tender joint counts at wdt Week 52 only
- Plasma for CZP concentration, anti-CZP antibodies, and for biomarkers at wdt Weeks 0, 12 and FU
- Concomitant medication at wdt Weeks 0, 12, 24 (and Q12W), 52 and FU

- AEs and IXRS (for the registration of visits) at wdt Week 0, 12, 24 (and Q12W), 52, and FU
- Other treatment administration at wdt Week 0. For Week 12 and 24 (and Q12W) the regimen of the particular medicine should be followed. If the Investigator choses to withdraw the subject, the local guidelines on initiation and monitoring of the particular treatment should be followed

9 ASSESSMENT OF EFFICACY

Most of these tools have been used in AS studies but early data support their use in axSpA as well (Barkham et al, 2009; Haibel et al, 2008).

9.1 Assessment of efficacy variables

9.1.1 Ankylosing Spondylitis Disease Activity Score (ASDAS)

The ASDAS is comprised of a number of assessments which are scored by the subject and physician and multiplied by a proven formula (van der Heijde et al, 2009) as listed:

0.121 x Back pain (BASDAI Q2 result, see Section 9.1.5)

0.058 x Duration of morning stiffness (BASDAI Q6 result)

0.110 x PGADA (see Section 9.1.13)

0.073 x Peripheral pain/swelling (BASDAI Q3 result)

0.579 x (natural logarithm of the CRP [mg/L] + 1)

Back pain, PGADA, duration of morning stiffness, peripheral pain/swelling and fatigue are all assessed on a numerical scale (0 to 10 units) (Lukas et al, 2009).

The variables related to ASDAS disease activity are defined as follows:

- ASDAS-Inactive Disease (ASDAS-ID): ASDAS <1.3
- ASDAS-Moderate Disease (ASDAS-MD): ASDAS ≥1.3, <2.1
- ASDAS-High Disease Activity (ASDAS-HD): ASDAS ≥2.1, ≤3.5
- ASDAS-very High Disease Activity (ASDAS-vHD): ASDAS >3.5

The variables related to ASDAS improvement are defined as follows:

- ASDAS-Clinically Important Improvement (ASDAS-CII): ASDAS reduction (improvement) of ≥1.1 relative to Baseline
- ASDAS-Major Improvement (ASDAS-MI): ASDAS reduction (improvement) of ≥2.0 relative to Baseline

The ASDAS will be calculated at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32 36, 40, 44, 48, and 52 (or at Withdrawal).

9.1.2 ASAS20, 40, ASAS 5/6 response, and ASAS partial remission

The ASAS20 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:

- PGADA (see Section 9.1.13)

- Pain assessment (the average of total and nocturnal spinal pain NRS scores)
- Function (represented by BASFI, Section 9.1.6)
- Inflammation (the mean of the BASDAI questions 5 and 6, [see Section 9.1.5] 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 ASAS criteria for 40% improvement are defined as relative improvements of at least 40%, and absolute improvement of at least 2 units on a 0 to 10 NRS in at least 3 of the 4 domains and no worsening at all in the remaining domain.

The ASAS 5/6 response is defined as at least 20% improvement in 5 of 6 domains, including spinal mobility (lateral spinal flexion) and CRP as more objective measures (Brandt et al, 2004).

The ASAS partial remission response is defined as a score of ≤2 units on a 0 to 10 unit scale in all 4 domains listed above for ASAS20.

The ASAS variables will be calculated at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 (or at Withdrawal).

9.1.3 ASAS-NSAID score

The ASAS-NSAID score is a tool that has been developed to measure the magnitude of NSAID intake during clinical studies (Dougados et al, 2011). In order to calculate the ASAS-NSAID score, the following information will be collected:

- Has there been NSAID intake since last visit?
- NSAID name
- Average daily intake (mg)
- Days with intake
  - <1 day/week
  - 1 to 3 days/week
  - 3 to 5 days/week
  - ≥5 days/week
  - Every day
- Starting date
- End date (or ongoing)

The general formula for calculation is as follows:

- (equivalent NSAID score) × (days of intake during period of interest) × (days per week)/(period of interest in days)

Each of the components of the above calculation are described below:

- Equivalent NSAID score: This is reported in terms of NSAID equivalent dose in mg/day on a 0 to 100 scale where the diclofenac 150mg equivalent is set to 100. An NSAID equivalence table was developed based on a survey of ASAS members. The table including the consensus equivalence score for various NSAIDs can be found in the Statistical Analysis Plan (SAP).
- Days of intake during period of interest: Equivalent to the total number of days covered during the period that is being measured.
- Days per week: Number of days per week when the NSAID is taken. This is collected in the categories described in the days with intake category listed above. Each category corresponds to a score as follows (score in parentheses):
  - Every day (7)
  - ≥5 days/week (6)
  - 3 to 5 days/week (4)
  - 1 to 3 days/week (2)
  - <1 day/week (0.5)
  - No NSAID intake (0)
- Period of interest in days: Refers to the number of days covered for a given NSAID. If only 1 NSAID was taken during the period of interest, this will be the same as days of intake during period of interest.

Dougados et al 2011, provided the following example. If during a period of interest (between 2 visits) of 6 months, the subject has taken piroxicam 20mg during 4 months and if during this 4 month period he has taken piroxicam 3 to 5 days per week the calculation is as follows:

- 100 (20mg piroxicam score) × 120 (4 months) × 4/7 (3 to 5 days/week)/180 (6 months) = 38.1

If the subject has used 10mg piroxicam during the remaining 2 months on 2 days a week, the NSAID score for this period is:

- 50 (10mg piroxicam score) ×60 (2 months) × 2/7 (1 to 3 days/week)/180 (6 months) = 4.8

In this example the total score for the 6 month period is 42.9 (38.1 plus 4.8).

9.1.4 ASQoL

The ASQoL, a validated disease-specific 18-item questionnaire, has been developed specifically for measuring HRQoL in subjects with AS (Doward et al, 2003). The ASQoL has been used and has shown to be responsive in axSpA (Barkham et al, 2009; Haibel et al, 2008). The ASQoL score ranges from 0 to 18 with higher score indicating worse HRQoL. A change of 1.8 points, which represents 10% of the possible score range, has been used as the minimal clinically important difference (MCID) criteria to guide the interpretation of ASQoL score changes in previous trials with a TNF-antagonist (van der Heijde et al, 2009; Davis et al, 2007). A change in ASQoL score of 2 points (ie, 10% of the total score range) will be used as the MCID to guide the interpretation of ASQoL score changes (see Appendix 18.4).

The ASQoL assessments per visit are described in Table 5–1.

9.1.5 BASDAI

The most common instrument used to measure the disease activity of AS from the subject's perspective is the BASDAI (Garrett et al, 1994). 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 (van Tubergen et al. Manuscript validating the response has been submitted and accepted by Rheumatology). The final BASDAI score ranges from 0 to 10, with lower scores indicating lower disease activity. The MCID used to interpret scores is 10mm on a VAS or 22.5% of the Baseline score (Pavy et al, 2005). An MCID of 1 unit will be selected for the NRS version (see Appendix 18.5).

The BASDAI 50 is defined as an improvement of at least 50% in the BASDAI response.

The BASDAI is calculated as follows:

$$\frac{Q1 + Q2 + Q3 + Q4 + \left(\frac{Q5+Q6}{2}\right)}{5}$$

Fatigue item of the BASDAI

Fatigue as a major symptom of AS can effectively be measured with single-item questions such as the BASDAI item (van Tubergen et al, 2002b). This item has shown moderate to good reliability and responsiveness (van Tubergen et al, 2002b). The same MCID will be used for the fatigue item of the BASDAI as for the total BASDAI score, ie, a change of 1 unit on the NRS.

The BASDAI assessments per visit are described in the schedule of study assessments Table 5–1.

9.1.6 BASFI

The BASFI is a validated disease-specific instrument for assessing physical function (van der Heijde et al, 2005; Calin et al, 1994). The BASFI comprises 10 items relating to the past week. The NRS version will be used for the answering options of each item on a scale of 0 ("Easy") to 10 ("Impossible") (van Tubergen et al [Manuscript validating the response has been submitted to Rheumatology] and van Tubergen et al, 2002a). The BASFI is the mean of the 10 scores such that the total score ranges from 0 to10, with lower scores indicating better physical function. The MCID used to interpret scores is 7mm on a 0 to 100mm VAS or 17.5% of the Baseline score (Pavy et al, 2005); an MCID of 1 unit will be used for the NRS version (see Appendix 18.6).

The BASFI assessments per visit are described in Table 5–1.

9.1.7 BASMI

The BASMI characterizes the spinal mobility of subjects with AS. The BASMI is a disease-specific measure consisting of 5 clinical measures to reflect subject axial status: cervical rotation; tragus to wall distance; lateral spinal flexion; modified Schober test; intermalleolar distance. Each of the 5 movements is scored according to the linear BASMI definition. The mean

of the 5 scores provides the BASMI score. The higher the BASMI score the more severe the subject's limitation of movement due to their axSpA.

The BASMI assessments per visit are described in Table 5–1.

9.1.8 Enthesitis (MASES)

The MASES is an index that measures the severity (ie, intensity and extent) of enthesitis through the assessment of 13 entheses (bilateral costochondral 1, costochondral 7, anterior superior iliac spine, posterior iliac spine, iliac crest and proximal insertion of the Achilles tendon sites, and the fifth lumbar vertebral body spinous process) (Heuft-Dorenbosch et al, 2003) each scored as 0 or 1 and then summed for a possible score of 0 to 13.

Enthesitis assessments per visit are described in Table 5–1.

9.1.9 Extra-articular assessments

The evolution of associated nonmusculoskeletal features including inflammatory bowel disease, psoriasis and uveitis (including their severity) and flare rate will be assessed as described Table 5–1.

9.1.10 Health status (EQ-5D)

The EQ-5D is comprised of a 5-item health status measures and a VAS. Each of the 5 health states is divided into 3 levels: no problem, some or moderate problems and extreme problems and is scored as 1, 2, and 3, respectively. The EQ-5D VAS records the respondent's self rated health status on a vertical 20 cm scale, 0 to 100 graduated (0=worst imaginable health status, 100=best imaginable health status) (see Appendix 18.7).

This instrument is to be completed by the subject as described in Table 5–1.

9.1.11 MOS Sleep Scale

The MOS Sleep Scale is a validated generic self-administered scale measuring specific aspects of sleep. The frequency with which each problem has been experienced during the previous 4 weeks is rated on a 6-point scale ranging from "none of the time" to "all of the time," except sleep quantity, which is reported in hours. All scores are transformed linearly to range from 0 to 100, again with the exception of the sleep quantity subscale, which is scored in hours. Higher scores indicate more of the attribute implied by the scale name (eg, more sleep disturbance, more adequate sleep, and greater sleep quantity). The psychometric properties of the MOS Sleep Scale have been found to be satisfactory by Hayes and colleagues (Hays et al, 2005). The domains of interest for this study are the Sleep Disturbance and the Sleep Problems Index II domains. The MCID for the Sleep Problems Index II is 6 points on a 0 to 100 scale (Wells et al, 2007) (see Appendix 18.8).

Subjects will be asked to complete the MOS Sleep Scale as described in Table 5–1.

9.1.12 MRI assessments

Magnetic Resonance Imaging according to the ASAS/Omeract definition is the presence of bone marrow oedema (BMO) or osteitis highly suggestive of SpA that is located in the typical anatomical areas (subchodral or periarticular bone marrow). There must be either more than 1 BMO lesion on 1 slice or a lesion that is present on at least two consecutive slices (Rudwaleit et al, 2009d). In practice this is very similar to the SPARCC SIJ ≥2 definition of MRI that requires

at least 2 BMO lesions to be present. A recent paper showed that the sensitivity and specificity of the ASAS/Omeract and SPARCC SIJ score ≥2 definitions of MRI positive were identical (sensitivity 0.80, specificity 0.76) (Weber et al, 2014). The Berlin modification of the ASspiMRI-a is a scoring system with a concentration on short-tau-inversion recovery (STIR) sequences without other fat saturation techniques (Braun and Baraliakos, 2011, Lukas et al, 2007; Braun and van der Heijde, and 2002; Braun et al, 2003). This scoring method quantifies changes in 23 vertebral units (VU) of the spine (from C2 to S1). A VU is defined as the region between 2 virtual lines through the middle of each vertebra. Active inflammation is scored by grading the degree of BMO from 0 to 3 in 1 dimension on 1 or more consecutive slices that represent the highest level of inflammation in a particular VU. Total spine ASspiMRI-a score in the Berlin modification can range from 0 to 69. In addition to the method mentioned above, MRIs may be evaluated using other reading criteria.

Magnetic resonance imaging of the spine and SI joints will be performed at Screening, Week 12 (SI only), 52, or Withdrawal Visit if MRI was performed more than 12 weeks prior to Early Withdrawal. MRIs will be assessed centrally and scoring will be done by 2 independent readers, who are blinded to both the order of the scans and to the treatment group, using a previously reported scoring system.

9.1.13 PGADA (NRS)

Subjects will score their global assessment of their disease activity in response to the question "How active was your spondylitis on average during the last week?" using a NRS where 0 is "not active" and 10 is "very active" (van Tubergen et al [manuscript submitted for publication]) (see Appendix 18.9).

The PGADA assessments per visit are described in Table 5–1.

9.1.14 PhGADA

The Investigator will assess the overall status of the subject with respect to the axSpA signs and symptoms and the functional capacity of the subject using a VAS where 0 is "very good, asymptomatic and no limitation of normal activities" and 100 is "very poor, very severe symptoms which are intolerable and inability to carry out all normal activities."

This assessment by the Investigator should be blinded.

The PhGADA will be completed as described in Table 5–1.

9.1.15 Productivity measures (Work Productivity Survey)

The WPS is an instrument used to assess productivity at work and within the home. The WPS has been found to be valid, reliable, and responsive to clinical changes in RA, PsA, and axSpA subjects (Osterhaus and Purcaru, 2014).

Site personnel should obtain information from the subject in order to complete this survey. The WPS is a 9-question instrument used to assess the impact of arthritis on productivity within and outside the home during the preceding 4 weeks. [redacted] on

a 0 to 10 scale (0=no interference; 10=complete interference).

[redacted]

on a 0 to 10 scale (0=no interference; 10=complete interference).

The WPS assessments per visit are described in Table 5–1.

9.1.16 Resources utilization

Study-specific questionnaires (standard CRF modules) will be used to capture data regarding resources utilization during the study, ie:

- Concomitant medical procedures
- Health care provider consultations not foreseen by the protocol
- Hospitalizations/emergency room visit

Site personnel should obtain information from the subject and also corroborate data with known AEs and SAEs in order to complete this survey as described in Table 5–1. The recall period for the questionnaire will be the previous 4 weeks.

9.1.17 SF-36

The SF-36 (version 2, standard recall) is a 36-item generic HRQoL instrument that uses a recall period of 4 weeks. Items are grouped into 8 domains as follows: Physical Functioning (10 items), Role Physical (4 items), Bodily Pain (2 items), General Health (5 items),Vitality (4 items), Social Functioning (2 items), Role Emotional (3 items), Mental Health (5 items), and 1 item for perceived stability or change in health (Health Transition) during the last year. The concepts represented by these domains contribute to physical, mental, and social aspects of HRQoL.

In addition to domain scores, the PCS and MCS scores are calculated from the 8 domains (excluding the Health Transition item). Component scores appreciate the impact of each domain on physical and mental health status (Ware et al, 1994). Each of the 8 domain scores and the component summary scores range from 0 to 100, with a higher score indicating a better health status. The 2 component summary scores are standardized with a mean of 50 and a standard deviation (SD) of 10 in the general USA population. The MCIDs for SF-36 domains and component summaries are 5 and 2.5 points, respectively (Strand et al, 2005) (See Appendix 18.10).

The SF-36 has been used and has shown to be responsive in axSpA (Haibel et al, 2008) and also validating in van Tubergen et al. (Manuscript validating the response has been submitted to Rheumatology). The SF-36 will be administered per visit as described in Table 5–1.

9.1.18 Spinal mobility

In addition to the assessments performed for the BASMI, additional spinal mobility assessments include:

- Occiput to wall distance
- Chest expansion

Spinal mobility will be assessed as described in Table 5–1.

9.1.19 Swollen and tender joint counts (44 joints evaluation)

The following 44 joints are to be examined for swelling and tenderness by the Principal Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. Preferably the same assessor should evaluate the subject at each arthritis assessment. The individual with this delegated duty must be listed on Form 1572.

Upper body (4) – bilateral sternoclavicular, and acromioclavicular joints

Upper extremity (26) – bilateral shoulders, elbows, wrists (includes radiocarpal, carpal and carpometacarpal bones considered as a single unit), metacarpophalangeals (MCPs) I, II, III, IV, and V, and thumb interphalangeals (IPs), and proximal IPs (PIPs) II, III, IV, and V

Lower extremity (14) – bilateral knees, ankles, and metatarsophalangeals (I, II, III, IV, and V)

The assessment for swelling and tenderness is made on 44 joints from the above list. Artificial and ankylosed joints are excluded from swelling and tenderness assessments.

The assessments per visit are described in Table 5–1.

Table 9–1: Swelling and tenderness grading

Grade	Swelling response (44)	Tenderness response (44)
0	None	None
1	Swelling present	Tenderness present

9.1.20 Total and nocturnal spinal pain NRS

The pain experienced by AS subjects is adequately measured by 2 separate questions: 1) total pain in the spine due to AS (ie, "How much pain of your spine due to spondylitis do you have?"); and 2) pain in the spine at night due to AS (ie, "How much pain of your spine due to spondylitis do you have at night?") (Sieper et al, 2009; van der Heijde et al, 2005; CPMP/EWP/556/95). Usually, a 10% difference (ie, a 1 point difference on a NRS ranging from 0 to 10) is considered the MCID used to interpret scores (Dworkin et al, 2008). Pain experienced by axSpA subjects has also been measured with this assessment (Haibel et al, 2008) and validated by van Tubergen et al (Manuscript validating the response has been submitted to Rheumatology) (see Appendix 18.11).

The pain NRS assessments per visit are described in Table 5–1.

10 ASSESSMENT OF PHARMACOKINETICS , EXPLORATORY BIOMARKERS, AND PHARMACOGENOMICS VARIABLE(S)

Plasma samples for the measurement of CZP concentrations will be taken at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52, and at the FU Visit (8 weeks after the Week 52/WD Visit). These plasma samples may be used additionally for analyses of CZP and its constituent moieties using alternative methods and the results of those analyses may be reported separately.

These plasma samples may be used for possible analyses of exploratory biomarkers, selected from the following list: MMP-3, BMP-2,-4 and -7, WNT1, WISP, Gremlin, DKK1, Sclerostin, Hedgehog proteins (Shh, Ihh, Dhh), Collagen turnover/cleavage products, collagen type X, VEGF, citrullinated vimentin fragments, cytokines: IL13, IL17 A and F, IL23, IL34, (TGF-β, M-CSF, GM-CSF, CSF-1, sCSF1r levels. The results of the analyses of CZP and its constituent moieties from alternative methods may be reported separately.

For subjects participating in the optional substudy, blood samples will be drawn for possible genetics/epigenetics, genomic, proteomics and metabolomic analysis at Baseline and Week 12, and for genomic, proteomics, and metabolomic analysis only, at Week 4 and Week 52 to enable exploratory evaluation of biomarkers relative to drug treatment, disease biology and inflammatory and immune response processes.

Samples will be moved from the Central Laboratory (ACM) at the end of the study to a long-term storage facility - BioStorage Technologies, GmbH - and will be stored at -80°C at a central biorepository for up to 20 years.

11 ASSESSMENT OF IMMUNOGENICITY VARIABLE(S)

Plasma samples for the measurement of anti-CZP antibodies will be taken at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52, and the FU Visit (8 weeks after the Week 52/WD Visit). The number and percent of subjects with anti-CZP concentrations above 2.4 units/mL will be reported as follows:

- At the time of each visit
- At any visit during treatment (not including post treatment withdrawal or FU visits)
- At any visit including post treatment withdrawal or FU visits

The sampling, handling, and shipment of samples will be performed as detailed in the Laboratory Manual.

12 ASSESSMENT OF SAFETY

12.1 Adverse events

12.1.1 Definition of adverse event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

If a surgical procedure is performed during the study participation, the underlying condition should be reported as the AE (eg, “appendicitis” is the AE resulting in appendectomy).

The following laboratory values and physical findings are also to be considered AEs:

- Laboratory value(s) that are out of reference range AND of clinical relevance, excluding Screening values
- Laboratory value(s) that change from a subject’s Baseline AND are of clinical relevance

- Pre-existing physical findings (including vital sign measurements) that worsen compared with Baseline AND that are "clinically important"

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after signing the informed consent form), including any Screening and FU Periods required by the protocol, must be reported in the CRF even if no IMP was administered but specific study procedures were conducted. This includes all AEs not present prior to the Screening Visit and all AEs which recurred or worsened after the Screening Visit.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or the Baseline Period.

12.1.2 Procedures for reporting and recording adverse events

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the Investigator should review any self assessment procedures (eg, questionnaires) employed in the study.

12.1.3 Description of adverse events

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The CRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event CRF (including judgment of relationship to study drug) are described in the CRF Completion Guidelines.

12.1.4 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

If an AE is still ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the Investigator must provide a justification. The follow up will usually be continued for 70 days after the subject has discontinued his/her IMP.

12.1.5 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"

- The AE verbatim term being the same for the first AE and AE verbatim term repeated including worsening, so that the repeated AE can be easily identified as the worsening of the first one

12.1.6 Pregnancy

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately notify UCB's Drug Safety (DS) department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as the pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an Early Withdrawal Visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the Early Withdrawal Visit.
- A FU Visit should be scheduled 8 weeks after the Week 52/WD visit.

The Investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form upon which the Investigator has to report the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the Investigator and filed at the site. UCB's DS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/CRO contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's DS department (for contact details see Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's DS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, therapeutic abortion, and unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE report form.

12.1.7 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the appropriate CRF module and drug accountability forms. Any SAE or nonserious AE associated with excessive dosing must be followed as any other serious or nonserious AE. These events may be symptomatic, in that the excessive dosing results in clinical signs and symptoms, or the excessive intake may itself be a symptom.

12.1.8 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the DS representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

12.2 Serious adverse events

12.2.1 Definition of serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- An important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious.
  Examples of important medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, infections that require treatment with parenteral antibiotics or the development of drug dependency or drug abuse.

  Confirmed active TB is an SAE and must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirements until such time as the TB infection resolves.
- Initial inpatient hospitalization or prolongation of hospitalization

A subject admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious (eg, life-threatening adverse experience, important medical event).

Hospitalizations for reasons not associated with the occurrence of an AE (eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner) do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.

Hospitalization for diagnostic or therapeutic procedures in the absence of any associated AE will not be considered as an SAE, except when otherwise required by regulatory authorities. If a hospitalization is planned prior to the subject receiving the first dose of IMP (at Week 0), it will not be classified as either an AE or SAE. This also applies to a scheduled elective surgery where no AE is present. A noncomplicated, preplanned elective surgery will not be considered an AE or SAE even if it involves hospitalization. However, if a hospitalization is unplanned or is a result of an AE, this will be considered to be an SAE.

12.2.2 Procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

It is important for the Investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE report form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each subject (which is usually the FU Visit), and to also inform participating subjects of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the current version of the CZP Investigator Brochure (IB).

12.2.3 Follow up of serious adverse events

An SAE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

Information on SAEs obtained after clinical database lock will be captured through the DS database without limitation of time.

12.3 Adverse events of interest

An AE of interest is any AE which is listed in the European Risk Management Plan, or meets another commitment requiring nonstandard expedited reporting, even if the AE does not fulfill the expedited reporting criteria of "serious," "unexpected," and "associated with the use of the drug." Adverse events of interest include:

- Serious infections including opportunistic infections
- Malignancies including lymphoma
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia
- Serious bleeding events
- Lupus and lupus-like illness
- Serious skin reactions (eg., Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

12.4 Immediate reporting of adverse events

The following AEs must be reported immediately:

- SAE: AE that the Investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of interest (see Section 12.3)

12.5 Laboratory measurements

Hematology, biochemistry, urinalysis, and CRP samples will be taken at Screening, Baseline, Weeks 2, 4, 8, 12, 24, 36, 52, and at the FU Visit (8 weeks after the Week 52/WD visit). Testing to rule out hepatitis B, hepatitis C, and HIV will be performed at Screening as well as the HLA-B27 antigen determination. Subjects will be encouraged to be in fasting condition at Baseline and at Week 52 or at the time the subject shifts to alternative treatment, for Apo-A1, ApoB, and lipoprotein(a) assessments.

The urinalysis will be performed with a dipstick, and in case of a positive outcome, on a clean catch urine sample sent to the central laboratory for analysis. The central laboratory will analyze and assess blood and urine samples for the following (except where indicated):

Table 12–1: Laboratory measurements

Hematology	Serum biochemistry	Urinalysis	Others
Red blood cells	Sodium	pH	Others
Hemoglobin	Potassium	Protein	Hepatitis B surface antigen
Hematocrit	Chloride	Glucose	Antibodies to hepatitis C
Platelets	Bicarbonate	Blood	Antibodies to HIV
White blood cells	Total calcium	Esterase	HLA-B27
Neutrophils	Inorganic phosphorus		
Lymphocytes	CRP		
Monocytes	Creatine phosphokinase[a]		
Eosinophils	Glucose	Microscopy (WBC, RBC, casts, crystals, bacteria) (Microscopy will be performed only when there are abnormalities on dipstick)	
Basophils	Creatinine	Urine-sample to be collected for central-laboratory analysis only when there are abnormalities on dipstick	
	Uric acid		

Table 12–1: Laboratory measurements

Hematology	Serum biochemistry	Urinalysis	Others
	Urea		
	Total protein		
	Albumin		
	Alkaline phosphatase		
	Aspartate aminotransferase		
	Alanine aminotransferase		
	Bilirubin		
	Total cholesterol		
	HDL[b]		
	LDL[b]		
	HbA1c[c]		

CRP=C-reactive protein; HbA1c=glycated hemoglobin; HDL=high density lipoprotein; HIV=human immunodeficiency virus; HLA-B27=human leukocyte antigen B27; LDL= low-density lipoprotein; RBC=red blood cells; WBC=white blood cells; ULN=upper limit of normal

[a] Creatine phosphokinase subtypes (CK-MM; CK-MB, and CK-BB) are required if the creatine phosphokinase measurement is >2 ULN

[b] HDL and LDL are to be measured every 6 months and at the time the subject shifts to open-label CZP.

[c] HbA1C is to be measure at Baseline and Week 52 or at the time the subject shifts to open-label CZP

12.6 Other safety measurements

12.6.1 Pregnancy testing

Pregnancy testing must be carried out for women of childbearing potential and will consist of serum testing at Screening and FU and urine testing (dipstick) at Baseline and Week 52/Withdrawal FU.

12.6.2 Physical assessments

Physical examination will be performed at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 24, 36, 52, and at the FU Visit (8 weeks after the Week 52/WD visit). Physical examination findings will be recorded in the CRF only at Screening. Clinically important abnormal changes in subsequent physical examinations will be recorded as AEs. Physical examinations must be documented in source documentation.

The following body systems will be examined:

- General Appearance
- Ear, nose and throat
- Eyes
- Hair and skin
- Respiratory
- Cardiovascular
- Gastrointestinal
- Musculoskeletal
- Hepatic
- Neurological (including limb reflexes)
- Mental Status

In addition the TB signs and symptoms will be assessed at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 24, 36, Completion at Week 52/Early Withdrawal Visit and FU (8 weeks after the Week 52/WD visit).

Weight is to be measured at Screening, Week 24, and at Completion at Week 52/Early Withdrawal. Height will be measured at the Baseline Visit only.

12.6.3 Assessment and management of TB and TB risk factors

As TNF-antagonists are known to be associated with significant risk of reactivation of latent TB, appropriate rigorous precautions are being taken within the protocol to address this (see Section 6.2 (Exclusion Criterion 16) and Section 6.3 (Withdrawal Criterion 6).

Signs and Symptoms

The Investigator should consider all potential sites of infection when assessing for TB during the subject's history and the physical examination, and other evaluations. Sites commonly infected by TB include: the lungs, larynx, lymph glands, pleura, gastrointestinal system, genito-urinary tract (including renal), bones and joints, meninges, peritoneum, pericardium, and skin. This is not an exhaustive list and unusual presentations and areas of involvement should always be considered.

Common symptoms that the subject may present with include cough, blood in sputum, night sweats, lymphadenitis, joint pain/swelling, spinal deformity, headache/confusion, abdominal pain mimicking IBD, frequent or painful urination, scrotal mass in men and pelvic inflammatory disease in women as well as other symptoms, or nonspecific symptoms. This is not an exhaustive list and unusual presentations should always be considered.

The subject may present an absence of signs, symptoms (ie, evidence of organ-specific involvement), or physical findings suggestive of TB infection with a positive IGRA test (or 2 indeterminate IGRA test results) and a chest x-ray (or other imaging) without evidence of TB infection. If the result of the IGRA test is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be randomized to study medication without further evaluation, treatment, and discussion with Study

Physician, if Latent TB infection is identified. (If active TB is identified, subject must undergo appropriate study-specified withdrawal procedures.) The retest must be done during the protocol-defined Screening window.

Note: If available, respiratory or other specimens must also be smear and culture negative for TB (CDC diagnosis of Latent TB infection [http://www.cdc.gov/TB/topic/testing/default.htm]).

Test Conversion

Tuberculosis test conversion is defined as a positive result (IGRA) for the current test but previous test results were negative (IGRA). All subjects with TB test conversion must immediately stop study drug administration. In case of a TB test conversion, the subject must be considered as having either a suspected new latent or an active TB infection and be promptly referred to an appropriate specialist (ie, pulmonologist, infectious disease specialist) must be consulted for further evaluation. If test conversion indicates latent TB infection, active TB, or nonmycobacterial TB infection then per UCB TB working instructions, TB test conversion (confirmed) should be classified as due to Latent TB infection, active TB infection, or NTMB infection. Additional assessments (eg, blood tests or IGRA test, chest x-rays or other imaging) should be performed as medically indicated.

Latent TB

In case the evaluation by the appropriate specialist indicates a new Latent TB infection, a prophylactic TB treatment (as described in Section 6.2, Exclusion Criterion 16) should be initiated and study medication can be continued no sooner than 4 weeks after start of prophylactic TB treatment, if it is deemed likely that prophylactic TB treatment is continued to completion by the Investigator.

If prophylaxis is not initiated, the subject must to be withdrawn.

Every action should be discussed in advance with the Medical Monitor. Latent TB must be reported as an SAE.

Active TB/NTMB

Subjects who develop active TB or NTMB infection during the study (conversion demonstrated by IGRA) must be immediately discontinued from study medication, and a withdrawal visit must be scheduled as soon as possible, but not later than the next regular visit. The subject should be encouraged to keep the FU Visit (8 weeks after the Week 52/WD visit). The TB must be documented as an SAE. Treatment for TB should be started based on local guidelines.

Note that subjects with history of or active NTMB infection are excluded from the study regardless of prior or current therapy.

Confirmed active TB is an SAE and an adverse event of special interest (AESI) and must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirement until such time as the TB infection resolves.

Subjects who prematurely discontinue treatment for latent TB, or, in the opinion of the Investigator or Sponsor, are noncompliant with anti-TB therapy must discontinue further use of study medication and be immediately withdrawn. Once withdrawn from study treatment,

subjects should return for the Study Completion/Withdrawal Visit, complete all Early Withdrawal assessments, and complete a FU Visit (8 weeks after the Week 52/WD-visit).

12.6.3.1 Tuberculosis assessments

During conduct of the study the TB assessment by IGRA will be performed at Screening and should be repeated at Week 52/Withdrawal for all subjects. The test results will be reported as positive, negative, or indeterminate and must be reviewed by an experienced TB specialist, radiologist, or a pulmonologist. If the assessment by IGRA is positive or indeterminate on retest for subjects who were previously negative at Screening and not treated for LTB, the subject may not continue study treatment without further evaluation by a TB specialist, prophylactic TB treatment, and discussion with the Medical Monitor, if LTB infection is identified. If active TB is identified, subject must undergo appropriate study specified withdrawal procedures. The retest must be done during the protocol-defined Screening window.

12.6.3.2 Chest x-ray

A plain posteroanterior chest x-ray (or, if done, computed axial tomography of the chest) must be done within 3 months prior to the Screening Visit. The chest x-ray must be clear of signs of TB infection (previous or current) before first study drug administration. The chest x-ray will be repeated at Completion Week 52/Withdrawal Visit (if chest x-ray was performed more than 12 weeks prior to Early Withdrawal Visit), only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

The chest x-ray (or, if done, Computed Axial Tomography of the Chest) must be negative for TB infection as determined by a qualified radiologist and/ or pulmonary physician. Any new clinically significant findings post-Baseline during physical exam or on chest x-ray must be documented in the source documents and CRF as an AE.

12.6.3.3 Quantiferon or Elispot testing

At Screening all subjects will have an IGRA test (QuantiFERON tube test or Elispot, if QuantiFERON test indicated is not available). The TB test will be repeated at Completion at Week 52/Early Withdrawal. Results of the tests will be reported as positive, negative, or indeterminate.

12.6.3.4 Tuberculosis questionnaire

The questionnaire “Evaluation of signs and symptoms of tuberculosis” should be used as a source document. The questionnaire will be completed at Screening, Baseline, and every 12 weeks thereafter including and up to Week 36 and at Completion at Week 52/Early Withdrawal Visit. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers “Yes” to the question “Has the subject been in close contact with an individual with active TB, or an individual who has recently been treated for TB?” at Screening is excluded. A “Yes” response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has latent or active TB (see Exclusion Criterion 16, Section 6.2). A “Yes” response to any of the

questions during the study should trigger further assessments to determine if the subject has either latent TB or active TB infection (see Appendix 18.12).

Subjects with a latent TB infection must receive prophylactic therapy prior to continuing study drug (if allowed by prophylactic therapy specific protocol).

Subjects with active TB infection must be withdrawn from the study and will have further assessments.

12.6.3.5 Tuberculosis management

For inclusion in the study, see Section 6.2 (Exclusion Criterion 16).

It is the Sponsor's requirement that all subjects who are on latent TB treatment at Baseline must comply with the full therapy course (see Section 6.2, Exclusion Criterion 16).

LTB infection and active TB identified during study

During the study, subjects who develop evidence of LTB infection or active TB must immediately stop further administration of study medication and will be referred to an appropriate TB specialist (pulmonologist or infectious disease specialist) for further evaluation. Evidence of LTB infection is defined as subject's IGRA test converts to positive or indeterminate (and confirmed indeterminate on repeat), or the subject's questionnaire or history and physical indicates that TB infection or exposure may have occurred. Evidence of active TB includes, in addition to the aforementioned tests, signs and symptoms of organ involvement. In either situation, the subject should be carefully assessed by a TB specialist for active TB. Subjects diagnosed with active TB or LTB infection should receive appropriate TB or prophylaxis therapy.

If a TB specialist excludes an active TB infection the subject can proceed with the study drug no earlier than 4 weeks after the start of an appropriate prophylactic therapy.
Any presumptive diagnosis or diagnosis of a TB infection is a reportable event. Confirmed active TB must be reported as an SAE; confirmed LTB as AESI (please see Section 12.2 and 12.3). The Investigator is to complete and submit the TB follow up form provided.

The subject should be transferred to the care of his/her physician and managed according to the best available standard of care. Subjects identified as having converted to active TB during the study must be withdrawn and scheduled to return for the Withdrawal Visit as soon as possible but no later than the next scheduled study visit and complete all Early Withdrawal Visit assessments.

The subject should be encouraged to complete a FU Visit (8 weeks after the Week 52/WD Visit).

If infection with NTMB is identified during the study, the same procedure as for active TB acquired during the study must be followed.

Subjects with LTB infection must not undergo IGRA testing. The IGRA test should be used for any protocol mandated monitoring.

Follow-up information of suspected and confirmed TB cases should be provided to UCB at least after 3, 9, and 12 months of the start date of anti-TB treatment, including hematological and biochemical safety parameters, x-ray evolution data, and TB diagnostic procedures used to follow up and confirm recovery of TB.

12.6.4 Vital signs

Subjects should be sitting for 5 minutes prior and during the collection of blood pressure, pulse rate, and respiration rate measurements.

Vital signs, including temperature will be measured at all on-site visits including the FU Visit (8 weeks after the Week 52/WD Visit) with the exception of the Week 1 Visit (respiration rate will be measured at Screening and Baseline only unless the subject has an AE).

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 Adherence to protocol

The investigator should not deviate from the protocol. However, the investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor.

After implementation of such measure, the Investigator must notify the CPM of the Sponsor within 24 hours and follow any local regulatory requirements.

13.2 Monitoring

UCB (or designee) will monitor the study to meet the Sponsor's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a CRO or a contract monitor.

The Investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review all CRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of CRFs, ensure that all protocol requirements, applicable authorities' regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

13.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self stick notes). Photocopies/printouts of electronic CRFs (eCRFs) are not considered acceptable source documents. Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other

printouts, completed scales, or Quality of Life Questionnaires, for example. Source documents should be kept in a secure, limited access area.

The following data will be recorded directly in the PC Tablet on site and will not appear in a source document as defined above:

- Patient outcome questionnaires: SF-36, EQ-5D-3L, OMERACT flare questionnaire, PGADA, WPS-RA and the socio-professional status
- Investigator's assessments: PhGADA and the swollen and tender joint counts

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the subject's source documents. The Investigator will authorize the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records such as MRI records must be saved and stored as instructed by UCB (or designee).

13.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, ECG tracings, x-ray films, laboratory notes). All data reported on the CRF should be supported by source documents, unless otherwise specified in Section 13.2.1.

13.3 Data handling

13.3.1 Case report completion

This study will be using remote data capture (RDC); the Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRF and in all required reports.

This study will also use an electronic device (Site Tablet) to capture the PhGADA and joint counts (see Section 13.4).

Serious adverse event reporting will be done using the SAE form (see Section 12.2) while also entering the event in the appropriate eCRF section. The safety database and the clinical database will be reconciled during the study and discrepancies will be corrected as needed.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF. Access to the RDC will be given after training has been received. A training certificate will be provided and filed.

Detailed instructions on the use of the RDC will be provided in the eCRF Completion Guidelines.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be re-approved by the Investigator. Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

13.4 Electronic reporting outcome

Compared to the paper patient questionnaires, the new electronic options have several advantages combining handheld devices in conjunction with online technologies in order to send subject self assessments directly to a central server. The collected data could then be reviewed in real time for monitoring of subject symptoms and compliance. The electronic patient reported outcome (ePRO) possibilities will be used in this study.

This study will use an electronic Site Tablet having a large screen and intuitive fingertip data entry to ensure all questionnaire data are captured appropriately, completely and on time. Not only subjects' data will be collected with the tablets, physicians' data (joint counts and PhGADA) will be entered directly.

Access to the system by site personnel will be given after training has been received. A training certificate will be provided and filed. The Investigator should maintain a list of personnel authorized to enter data into the electronic ePRO device.

13.5 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data monitoring system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Case Report form data are entered into the clinical database by site personnel.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

13.5.1 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The Investigator will keep a list containing all subjects enrolled into the study. This list remains with the Investigator and is used for unambiguous identification of each subject. The list contains the subject identification number, full name, date informed consent signed, date of screening, and the hospital number or National Health Security number, if applicable.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

13.6 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC also should be informed and provided with reason(s) for the

termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused study drug and other material in accordance with UCB procedures for the study.

Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator, as appropriate:

- Return of all study data to the Sponsor or its representative
- Data clarification and/or resolution
- Accountability, reconciliation, and arrangements for used and unused study drugs
- Review of site study records for completeness
- Discussion/reminder on archiving responsibilities

Further details will be given in the monitoring guidelines.

13.7 Archiving and data retention

The Investigator will maintain adequate records for the study, including CRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's study master file.

13.8 Audit and inspection

The Investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform UCB (or designee).

13.9 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

14 STATISTICS

A description of statistical methods follows and will be described in more detail in the SAP.

14.1 Definition of analysis sets

The Enrolled Set (ES) will consist of all subjects who have given informed consent.

The Randomized Set (RS) will consist of all subjects randomized into the study.

The Safety Set (SS) will consist of all subjects in the RS who have received at least 1 dose of study medication.

The Full Analysis Set (FAS) will consist of all subjects in the RS who have received at least 1 dose of study medication and who have a valid Baseline efficacy measurement for ASDAS.

The Per-Protocol Set (PPS) will consist of subjects in the FAS without any important protocol deviations that may influence the validity of the primary efficacy data. The PPS may also require that a defined period of exposure to study medication be completed. Important protocol deviations will be predefined and evaluated prior to study unblinding/database lock.

14.2 General statistical considerations

All efficacy analyses will be performed using the FAS. The PPS will be used for a sensitivity analysis on the primary endpoint only.

The statistical analysis of the primary efficacy variable and selected secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure. The predefined order of hypothesis testing, each at a 2-sided 0.05 significance level for the comparison between CZP 200mg Q2W and placebo, will be performed in the sequence shown below. After the first test, each subsequent test is performed only if the previous test is significant in favor of CZP at the 2-sided 0.05 level. Note that the first test relates to the primary efficacy variable while the others provide the sequence testing for the secondary efficacy variables.

1. ASDAS-MI response at Week 52
2. ASAS40 response at Week 12
3. Change from Baseline in BASDAI at Week 12
4. Change from Baseline in BASFI at Week 12
5. ASAS40 response at Week 52
6. Change from Baseline in BASDAI at Week 52
7. Change from Baseline in BASFI at Week 52
8. Change from Baseline in SI joint SPARCC score at Week 12

Variables evaluated over time will be summarized using imputed and observed case values. Further details on data summarization will be provided in the SAP.

14.3 Planned efficacy analyses

The primary efficacy variable measurement for this study is based on ASDAS-MI response at Week 52. The associated primary outcome of the study will be defined as a composite endpoint that is achieved if a subject fulfills the following 2 components:

1. Remain in the study and on study treatment through 52 weeks
2. Achieve an ASDAS-MI response at 52 weeks

For simplicity, this primary efficacy variable will be referred to as ASDAS-MI response at Week 52. However, the composite definition as described above will apply when this endpoint is analyzed. The primary analysis for this endpoint will be based on logistic regression. The odds ratio of the ASDAS-MI responder rates at Week 52 will be estimated and tested between treatment groups using a logistic regression model with factors of treatment group, region, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+). If the logistic regression model is unable to converge, then MRI/CRP classification may be dropped from the model to facilitate convergence. The study design is likely to result in some sites with a small number of enrolled subjects. The use of region as a stratification variable and as a factor in the model is intended to combine study centers in similar geographic regions. The geographic regions to be used will be defined in the IXRS and in the SAP. Given the composite endpoint definition described above, there will be no missing data for the primary endpoint, as subjects that discontinue study treatment prior to Week 52 or who do not have an ASDAS-MI status at Week 52 are considered nonresponders to study treatment.

As described in Section 6.3, subjects who discontinue study treatment will not necessarily be withdrawn from the study. In an attempt to minimize missing data, efforts will be made to continue to collect safety and efficacy data on these subjects through study completion. An alternative analysis for ASDAS-MI at Week 52 will be performed in which the observed data at Week 52 will be used, regardless of whether or not the subject is still on his/her randomized study treatment at that time. Despite efforts to continue to collect data on all subjects (even if they discontinue study treatment), there may still be subjects with missing data at Week 52. Such subjects will be considered as nonresponders in accordance with the composite endpoint definition outlined above. The same logistic regression model specified for the primary analysis will be used.

Subgroup analyses by age, gender, race, symptom duration, smoking history, HLA-B27 genotype, anti-CZP Ab status, region, prior anti-TNF exposure, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) will be performed for the primary variable.

14.4 Secondary efficacy analyses

The changes from Baseline in BASDAI and BASFI at Week 12 and Week 52 are specified as secondary efficacy variables. As these are continuous variables, missing data must be handled using a different approach from what is specified for the primary efficacy endpoint (a responder variable).

Investigators will be given discretion to discontinue study treatment for subjects not responding in order to provide them with alternative therapy to treat the condition. Therefore, in many cases, missing efficacy data due to study treatment discontinuation should be dependent on the observed efficacy scores, but independent of unobserved data. This would be consistent with a missing at random pattern of missingness. However, the possibility of discontinuation due to tolerability or other unobserved data cannot be completely discounted. Therefore, a missing not at random mechanism will be considered as the primary analysis method of continuous secondary efficacy variables, where reference-based imputation methods will be used.

This approach will impute missing data as well as data at time points following discontinuation of study treatment for both the CZP and placebo groups using an imputation model developed based on data from the placebo group (Mallinckrodt, 2013). The estimand being evaluated in this case is a de-facto estimand that has been described as the difference in outcome improvement in all randomized subjects at the planned endpoint attributable to the initially randomized medication (Mallinckrodt, 2012). This reference-based imputation procedure will be described in greater detail in the SAP. The final model to be used on the imputed data will be an analysis of covariance (ANCOVA) model where response is the change from Baseline, with Baseline score as a fixed-effect covariate and treatment group, region, and MRI/CRP classification as fixed-effect categorical factors.

Additionally, change from Baseline in SI joint SPARCC score at Week 12 is a continuous secondary efficacy variable. As with BASDAI and BASFI, a reference-based imputation approach will be used to account for missing data. However, it should be noted that, unlike BASDAI and BASFI, SPARCC score will not be measured at any time points between Baseline and Week 12, meaning that those are the only 2 time points that can be considered in the evaluation of SPARCC score at Week 12. Therefore, Week 12 represents the only time point at which the placebo treatment effect can be evaluated for the imputation procedure. Comparisons between treatment groups will be made using an ANCOVA on the imputed data set. The model will include Baseline score, treatment group, region, and MRI/CRP classification.

The ASAS40 response at Week 12 and Week 52 are responder secondary efficacy endpoints. As a responder variable, ASAS40 will be analyzed using logistic regression based on a model similar to the one described for the primary analysis. As with the primary efficacy endpoint, the ASAS40 will be treated as a composite endpoint when it is analyzed. Specifically, subjects will need to 1) achieve the relevant response (ASAS40) and 2) remain in the study and on their randomized study treatment through the time point being analyzed (Week 12 or Week 52).

The comparison of CZP 200mg Q2W to placebo as described above for the ASAS40 response, BASDAI, and BASFI at Week 12 and Week 52 and for SI joint SPARCC score at Week 12 will be part of the fixed sequence testing procedure outlined in Section 14.2.

Additionally, sensitivity analyses will be conducted on these secondary efficacy endpoints. In particular, the assumptions related to missing data will be investigated further. These analyses are described in Section 14.8.

An additional secondary efficacy variable is the number of subjects with relevant changes to background medication. This variable will be based on whether or not subjects take certain pre-specified background medications during the course of the study and will be defined in the

SAP. The analysis for this variable will use the same logistic regression model described for the primary variable.

14.5 Other efficacy analyses

Treatment group comparisons for CZP 200mg Q2W vs placebo will be performed based on the change from Baseline in other selected efficacy variables. These analyses will be performed using an ANCOVA model including Baseline score, treatment group, region, and MRI/CRP classification. The treatment differences and corresponding 95% confidence intervals will be calculated based on the adjusted means. Missing values or values observed after discontinuing study treatment will be imputed using last observation carried forward (LOCF). The following variables will be analyzed in this manner:

- PGADA
- Morning stiffness (average of BASDAI questions 5 and 6)
- BASMI
- Total and nocturnal spinal pain
- SF-36, PCS, MCS, and individual domains
- Fatigue NRS
- ASQoL
- Sleep Problems Index II domains of the MOS Sleep scale

Statistical analyses will also be done for BASDAI, BASFI, and SI joint SPARCC score for time points not specified in the secondary efficacy analyses, using the same analysis methods described in Section 14.4. Additionally, ASDAS and ASAS response variables will be analyzed using a logistic regression model similar to the one specified for the primary analysis at time points not covered in the primary and secondary efficacy analyses.

These comparisons are not part of the multiplicity-controlled testing procedure described in Section 14.2. The p-values reported for these analyses will not be adjusted for multiplicity and will be considered nominal. Exploratory statistical comparisons for CZP 200mg Q2W vs placebo will also be performed for WPS scores using the nonparametric bootstrap-t method. This will be explained in greater detail in the SAP.

Summary statistics will be provided for other variables. Summary statistics will consist of frequency tables and percentages for categorical variables. Continuous variables will be summarized by visit (where applicable) with descriptive statistics (number of available observations [n], mean, median, SD, minimum and maximum). Details on the analysis of the other endpoints will be provided in the SAP.

14.6 Planned safety and other analyses

14.6.1 Safety analyses

The frequency of all AEs during the study period will be presented for each treatment group separately by system organ class, high level term, and preferred term. The data will be displayed

as number of subjects experiencing the AEs, percentage of subjects, and number of AEs. Data will also be corrected for exposure and reported by 100 patient-years.

Since subjects will be permitted to change background medications and because they may also discontinue study treatment and initiate a new treatment (including biologics) during the course of the study, special consideration will be given to how AEs are attributed to study treatment. This, along with other specialized AE summaries, will be described in greater detail in the SAP.

Laboratory evaluations and vital signs will be analyzed over time in the SS for observed cases and at the end of treatment.

14.6.2 Pharmacokinetic and immunogenicity variable analysis

Certolizumab pegol plasma concentrations will be tabulated and summarized by treatment group (overall and by anti-CZP Ab level - above or below 2.4 units/mL within each treatment group) for each visit at which samples were taken using the geometric mean, geometric coefficient of variation, 95% confidence intervals (CIs), arithmetic mean, arithmetic SD, minimum and maximum, geomean plasma concentration time curves with their 95% CI will be plotted overall and by anti-CZP Ab status.

The number and percent of subjects with titre above 2.4 units/mL will be presented for each visit, at any visit during treatment (not including post treatment withdrawal or FU visits) and at any visit including post treatment withdrawal or FU visits. For the subjects with at least 1 anti-CZP Ab titre above 2.4 units/mL, the first timepoint of occurrence of the titre above 2.4 units/mL will also be displayed.

In addition, safety and efficacy profiles by anti-CZP Ab level will be investigated.

14.7 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on study conduct or on the primary efficacy outcome for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented prior to unblinding to confirm exclusion from analysis sets.

14.8 Handling of dropouts or missing data

For analysis purposes, the primary efficacy variable is defined as a composite endpoint in which it is necessary to achieve ASDAS-MI at Week 52 and to remain on randomized study treatment through Week 52 in order to be considered a responder (see Section 14.3). Because this composite endpoint definition does not allow for a missing response status, no formal method for handling missing data is needed in the primary analysis. An additional analysis (also described in Section 14.3) will be performed in which all observed data at Week 52 are used, including data collected for subjects who may have discontinued study treatment without being withdrawn from the study.

Analyses of other binary efficacy variables will be treated in the same way as the primary efficacy variable. That is, a subject will be considered a responder only if the response is achieved and if the subject is still on his/her randomized study treatment at the time when the variable is evaluated. For ASAS40 response at Week 12 and Week 52 (secondary efficacy

endpoints included in the fixed sequence statistical testing procedure), an additional analysis based on all collected data (as described above for the primary endpoint) will be performed.

To account for missing data and data following discontinuation of study treatment for continuous secondary efficacy variables (change from Baseline in BASDAI and BASFI at Week 12 and Week 52 and change from Baseline in SI joint SPARCC score at Week 12), the analysis method that will be used when considering statistical significance in the fixed sequence testing procedure will be referenced-based imputation where an ANCOVA model is used on the multiply imputed data (see Section 14.4).

Other analyses of continuous secondary efficacy data will be implemented to evaluate sensitivity of results to the method of handling missing data and will include the following:

- ANCOVA based on all observed data (including from subjects who discontinued study treatment but continued in the study) where any remaining missing data is imputed using reference-based imputation methods
- mixed model for repeated measures (MMRM) with Baseline score as a fixed effect covariate and treatment group, region, MRI/CRP classification, and visits as fixed effect categorical factors, and Baseline by visit and treatment group by visit as interaction terms (where data following study treatment discontinuation are treated as missing)
- LOCF
- Baseline observation carried forward (BOCF)

Additionally, "tipping point" sensitivity analyses will be conducted. These analyses will vary assumptions about average outcomes among the subjects in the CZP treatment group who discontinue study treatment early through a series of delta adjustments (O'Kelly, 2014). These assumptions may be severe and will include the possibility that subjects with missing data in the CZP treatment group had worse outcomes than dropouts on the placebo arm. Such adjustments to the assumptions may be performed until a statistically significant result in favor of CZP is no longer observed. The plausibility of the assumptions leading to that change would then be considered. Further details on all of these sensitivity analyses will be provided in the SAP.

Descriptive summaries based on observed case data will also be prepared.

Additionally, algorithms for imputing missing or partial dates for safety evaluations will be detailed in the SAP.

14.9 Planned interim analysis and data monitoring

Regular monitoring of safety data collected during clinical studies will be performed as described in the Safety Signal Detection in the Ongoing Clinical Trials Charter for CZP.

A specific data monitoring, steering, or evaluation committee is not planned for this study.

14.10 Determination of sample size

Subjects will be randomized in a 1:1 ratio to the CZP 200mg Q2W and placebo treatment groups. The expected response rates for ASDAS-MI at Week 52 are 40% and 20% for CZP and placebo, respectively. A total sample size of 300 (150 subjects per treatment group) provides

95% power to detect a statistically significant difference in the ASDAS-MI response rate at Week 52 between CZP and placebo, using a 2-sided significance level of 0.05.

15 ETHICS AND REGULATORY REQUIREMENTS

15.1 Informed consent

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the written Informed Consent form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection. An additional Informed Consent form for participation in the substudy should be completed.

If the Informed Consent form is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

All studies conducted at centers in the USA must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent form. A CRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

15.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject. The Investigator will fill in the subject identifying information and medical emergency contact information. The Investigator will instruct the subject to keep the card with them at all times.

15.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to

initiation of the study, the Investigator/UCB will forward copies of the protocol, Informed Consent form, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

15.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at Screening.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

15.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

16 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements, as applicable.

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18 APPENDICES

18.1 ASAS classification criteria for axial SpA

ASAS classification criteria for axial SpA

(for subjects with chronic back pain ≥3 months and age at onset <45 years)

Imaging criteria	ASAS clinical criteria for axial SpA
Sacroiliitis (MRI or radiographs*) plus ≥1 SpA feature	HLA-B27 plus ≥2 other SpA features

SpA features**	
Inflammatory back pain***	Psoriasis
Arthritis	Crohn's disease/ulcerative colitis
Enthesitis (heel)	HLA-B27
Uveitis	Elevated CRP
Dactylitis	

CRP=C-reactive protein; MRI=magnetic resonance imaging; HLA-B27=human leukocyte antigen B27; NSAID=nonsteroidal anti-inflammatory drug; SpA=spondyloarthritis

* Active inflammatory lesions of sacroiliac joints with definite bone marrow oedema/osteitis suggestive of sacroiliitis associated with spondyloarthritis in MRI or radiographic sacroiliitis grade 2 to 4 bilaterally or grade 3 to 4 unilaterally according to modified NY criteria.
** Family history for SpA and Good response to NSAIDs are excluded as SpA feature criteria.
***Inflammatory back pain according to ASAS criteria for Axial SpA defined as the presence of 4 out of 5 of the following parameters:

1) age at onset <40 years
2) insidious onset
3) improvement with exercise
4) no improvement with rest
5) pain at night (with improvement upon getting up)

18.2 Modified NY criteria for ankylosing spondylitis

Subjects meeting the NY criteria in the context of this protocol are defined as subjects meeting the definite AS diagnosis according to the modified NY criteria below.

Modified NY criteria for ankylosing spondylitis

Diagnosis
1) Clinical criteria
a) Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest.
b) Limitation of motion of the lumbar spine in both the sagittal and frontal planes.

Modified NY criteria for ankylosing spondylitis

Diagnosis
c) Limitation of chest expansion relative to normal values corrected for age and sex.
2) Radiologic criterion
Sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3 to 4 unilaterally.
Grading
1) Definite ankylosing spondylitis if the radiologic criterion is associated with at least 1 clinical criterion

Note: A second grading of "probably ankylosing spondylitis" is part of the modified NY criteria, but it is not applicable for this study. It is included here for completeness. The grading will be probable ankylosing spondylitis if three clinical criteria are present and the radiologic criterion is present without any signs or symptoms satisfying the clinical criteria (other causes of sacroiliitis should be considered).

18.3 Table of corticosteroid equivalent doses

Table of corticosteroid equivalent doses

Prednisone (reference)	10mg
Cortisone	50mg
Hydrocortisone	40mg
Prednisolone	10mg
Triamcinolone	8mg
Methylprednisolone	8mg
Betamethasone	1.5mg
Dexamethasone	1.5mg

Corticosteroid equivalent doses (with reference to prednisone 10mg dose) (Meikle and Tyler, 1977)

The following information (eg, questionnaire) is copyrighted and UCB does not have permission to disclose the contents.

18.9 PGADA (NRS)

NRS patient global disease activity

How active was your spondylitis on average during the last week?

Please tick the box that represents your answer (i.e. [X] 10)

0	1	2	3	4	5	6	7	8	9	10

Not active very active

The following information (eg, questionnaire) is copyrighted and UCB does not have permission to disclose the contents.

18.11 Total spinal pain NRS and nocturnal spinal pain NRS

NRS pain
Please tick the box that represents your answer (i.e. [10])

1. Total Spine Pain
   How much pain of your spine due to spondylitis do you have?

0	1	2	3	4	5	6	7	8	9	10

no pain — most severe pain

2. Nocturnal Spine Pain
   How much pain of your spine due to spondylitis do you have at night?

0	1	2	3	4	5	6	7	8	9	10

no pain — most severe pain

18.12 Tuberculosis Worksheet

Tuberculosis Worksheet (Source)

Evaluation for signs and symptoms of tuberculosis questionnaire

The following questions are to be asked of every subject for evaluation of risk factors for tuberculosis (TB). Responses to each question must be documented on this source document.

- Has the patient been in close contact (i.e., sharing the same household or other enclosed environment) with an individual with active TB or an individual who has recently been treated for TB? ☐ Yes ☐ No
- Does the subject have a new cough lasting more than 14 days or a change in a chronic cough? ☐ Yes ☐ No
- Does the subject have night sweats? ☐ Yes ☐ No
- Does the subject have a persistent fever? ☐ Yes ☐ No
- Does the subject have unintentional weight loss (more than 10% of body weight)? ☐ Yes ☐ No
- Is the subject [or subject's parents/legally acceptable representative(s) if subject is a minor] a hospital employee or in frequent contact with hospital employees (example: providing catering service to hospital employees or married to one)? ☐ Yes ☐ No
- Is the subject frequently exposed to other subjects (study visits/ hospitalizations) that are on study drug or other immunosuppressive drugs? ☐ Yes ☐ No
- Does the subject reside in, did the subject ever reside in, or is the subject frequently traveling to a TB endemic region(s)? ☐ Yes ☐ No
- Does the subject reside in, did the subject ever reside in, or is the subject frequently visiting densely populated areas such as highly urbanized city centers? ☐ Yes ☐ No
- Does the subject frequently use public transportation? ☐ Yes ☐ No
- Is the subject in frequent contact with elderly or underprivileged populations (homeless or other people needing social assistance)? ☐ Yes ☐ No
- Does the subject appear malnourished? ☐ Yes ☐ No
- Has the subject had an abnormal chest x-ray since the last evaluation? ☐ Yes ☐ No

(v.2009-09-09)

19 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subInvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

20 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate efficacyand safety of certolizumab pegol in subjects with active

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	01-Jun-2015 18:08 GMT+02
[redacted]	Clinical Approval	01-Jun-2015 19:31 GMT+02

PROTOCOL AS0006 (C-AXSPAND) AMENDMENT 4

PHASE 3, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO EVALUATE EFFICACY AND SAFETY OF CERTOLIZUMAB PEGOL IN SUBJECTS WITH ACTIVE AXIAL SPONDYLOARTHRITIS (AXSPA) WITHOUT X-RAY EVIDENCE OF ANKYLOSING SPONDYLITIS (AS) AND OBJECTIVE SIGNS OF INFLAMMATION

PHASE 3

EudraCT Number: 2015-001894-41

IND Number: 9,869

UCB BIOSCIENCES GmbH
Alfred-Nobel-Strasse 10
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GERMANY

Protocol/Amendment number	Date	Type of amendment
Final Protocol	01 Jun 2015	Not applicable
Protocol Amendment 0.1 (Taiwan)	02 Sep 2015	Substantial
Protocol Amendment 1	15 Dec 2015	Substantial
Protocol Amendment 1.1 (Taiwan)	12 Jan 2016	Substantial
Protocol Amendment 2	14 Mar 2016	Substantial
Protocol Amendment 2.1 (Taiwan)	22 Apr 2016	Substantial
Protocol Amendment 3	13 Feb 2017	Substantial
Protocol Amendment 3.1 (Taiwan)	24 Mar 2017	Substantial
Protocol Amendment 3.2 (Australia)	28 Apr 2017	Substantial
Protocol Amendment 4	19 Dec 2017	Substantial

Confidential Material

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SERIOUS ADVERSE EVENT REPORTING

Serious Adverse Event reporting (24h) and safety related issues	
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E-Mail	**DS_ICT@ucb.com**

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LIST OF ABBREVIATIONS

ABA	abatacept
ACR	American College of Rheumatology
ADA	adalimumab
ADAb	anti-drug antibody (also called anti-CZP antibody)
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
Anti-CZP Ab	anti-CZP antibody
Apo	apolipoprotein
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASAS20, 40	Assessment of SpondyloArthritis International Society 20%, 40% response criteria
ASAS5/6	Assessment of SpondyloArthritis International Society 20% improvement in 5 of 6 domains
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASDAS-CII	Ankylosing Spondylitis Disease Activity Score clinically important improvement
ASDAS-HD	Ankylosing Spondylitis Disease Activity Score high disease activity
ASDAS-ID	Ankylosing Spondylitis Disease Activity Score inactive disease
ASDAS-MD	Ankylosing Spondylitis Disease Activity Score moderate disease
ASDAS-MI	Ankylosing Spondylitis Disease Activity Score major improvement
ASDAS-vHD	Ankylosing Spondylitis Disease Activity Score very high disease activity
ASQoL	Ankylosing Spondylitis Quality of Life
ASspiMRI-a	Ankylosing spine MRI acuity
AU	anterior uveitis
axSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMO	bone marrow oedema
BMP	bone morphogenetic protein
BOCF	Baseline observation carried forward
CDMS	clinical data monitoring system

CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COX-2	cyclooxygenase 2
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRF	case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CSF-1	colony-stimulating factor-1
CZP	certolizumab pegol
Dhh	Dessert hedgehog
DKK1	Dickkopf-related protein 1
DMARD	disease-modifying antirheumatic drug
DS	Drug Safety
ECG	electrocardiogram
eCRF	electronic Case Report Form
ePRO	electronic patient reported outcome
EQ-5D	EuroQoL Health Status Questionnaire (5 dimensions)
ES	Enrolled Set
ETN	etanercept
EU	European Union
FAS	Full Analysis Set
FU	Follow-Up
GCP	Good Clinical Practice
GM-CSF	granulocyte macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
GOL	golimumab
HbA1c	Hemoglobin A1c
HCQ	hydroxychloroquine
HIV	human immunodeficiency virus
HLA-B27	human leukocyte antigen B27
HRQoL	health-related quality of life
ia	intra-articular
IB	Investigator Brochure

IBD	inflammatory bowel disease
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFX	infliximab
IGRA	Interferon-Gamma Release Assay
Ihh	Indian hedgehog
IL	interleukin
IMP	investigational medicinal product
IP	interphalangeal
IRB	Institutional Review Board
iv	Intravenous(ly)
IXRS	interactive response system
LOCF	last observation carried forward
LTB	latent tuberculosis
M-CSF	Macrophage colony-stimulating factors
MAR	missing at random
MASES	Maastricht Ankylosis Spondylitis Enthesitis Score
MCID	minimal clinically important difference
MCMC	Markov Chain Monte Carlo
MCP	metacarpophalangeal
MCS	Mental Component Summary
MedDRA®	Medical Dictionary for Regulatory Activities®
MI	multiple imputation
MMP-3	matrix metalloproteinase-3
MMRM	mixed model for repeated measures
MOS	Medical Outcomes Study
MRI	magnetic resonance imaging
mNY	Modified New York (criteria)
MTX	methotrexate
nr-axSpA	nonradiographic axSpA
NRS	Numerical Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
NTMB	nontuberculous mycobacteria
NYHA	New York Heart Association

OMERACT	Outcome Measures in Rheumatology Clinical Trials
PCS	Physical Component Summary
PFS	prefilled syringe
PhGADA	Physician's Global Assessment of Disease Activity
PGADA	Patient's Global Assessment of Disease Activity
PIP	Proximal IP
PK	pharmacokinetics
PPS	Per Protocol Set
prn	as needed
PsA	psoriatic arthritis
Q2W	every 2 weeks (every other week)
Q12W	every 12 weeks
QoL	Quality of Life
RA	rheumatoid arthritis
RDC	remote data capture
RS	Randomized Set
SAA	Spondylitis Association of America
SAARD	slow-acting antirheumatic drug
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
sCSF1r	soluble colony-stimulating factor-1 receptor
SD	standard deviation
SF-36	Short-Form 36-Item Health Survey
SFE	Safety Follow-Up Extension
SFE-SS	Safety Follow-Up Extension-Safety Set
Shh	Sonic hedgehog
SI	sacroiliac
SIJ	sacroiliac joint injection
SOP	standard operating procedure
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SPARTAN	Spondyloarthritis Research and Treatment Network
SPC	Summary of Product Characteristics

SS	Safety Set
SSCM	Single Safety Case Management
SSZ	sulfasalazine
STIR	short-tau-inversion recovery
TB	tuberculosis
TGF	transforming growth factor
TNF	tumor necrosis factor
TNFi	tumor necrosis factor-alpha inhibitor
ULN	upper limit of normal (for CRP the ULN defined as the upper limit of normal value indicative for inflammatory disease)
USA	United States of America
VAS	visual analog scale
VEGF	vascular endothelial growth factor
VU	vertebral units
WBC	white blood cell
WD	Withdrawal
wdt	withdrawal treatment
WISP	wingless-related mouse mammary tumor virus integration site protein (WNT1)-inducible signaling pathway proteins
WNT1	wingless-related mouse mammary tumor virus integration site protein
WPS	Work Productivity Survey

1 SUMMARY

The C-axSpAnd study (AS0006) is a randomized, double-blind, parallel-group, placebo-controlled study, consisting of 52 weeks of treatment with certolizumab pegol (CZP) and a Follow-Up (FU) Period of 8 weeks after the Week 52 visit. The study population is subjects with active axial spondyloarthritis (axSpA) without x-ray evidence of ankylosing spondylitis (AS), but either with sacroiliitis on magnetic resonance imaging (MRI) or C-reactive protein (CRP) levels indicative of inflammatory disease or both, who have had an inadequate response to, have a contraindication to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

The study population will be subjects (≥18 years), with a documented diagnosis of adult-onset axSpA and who meet the Assessment of SpondyloArthritis International Society ([ASAS], Sieper et al, 2009) criteria for axSpA, who have had back pain of at least 12 months' symptom duration, and with active disease defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and spinal pain ≥4 on a 0 to 10 Numerical Rating Scale (NRS). At Baseline, evidence of inflammatory disease will be confirmed either by presence of sacroiliitis on MRI (according to ASAS/Outcome Measures in Rheumatology Clinical Trials [OMERACT] criteria) or by elevated CRP or by presence of both.

Additionally, subjects must have had an inadequate response to, have a contraindication to, or have been intolerant to at least 2 NSAIDs. Inadequate response to a NSAID is defined as lack of response to at least 14 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID. Eligible subjects will be allocated to the following double-blind study treatments in a 1:1 ratio:

- CZP administered subcutaneously (sc) at the dose of CZP 400mg at Weeks 0, 2, and 4 followed by CZP 200mg every 2 weeks (every other week; Q2W) sc (starting at Week 6)
- Placebo

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site. At the Week 0, 2, 4, 6, and 8 visits, the administration must be done by dedicated, unblinded, and adequately trained site personnel. At the Week 10 and 12 visits, the subject will receive training on self-injection and the study treatment will be self-administered under the supervision of the unblinded study personnel. At Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50, the study treatment administration should preferably be done by the unblinded study personnel, or alternatively by self-injection of the subject under the supervision of the unblinded study personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46.

The study will be placebo controlled for 52 weeks and will allow changes in background medications as required to control disease activity according to the judgment of the Investigator.

Subjects whose disease activity cannot be controlled by study medication and changes in background therapy (including and not limited to analgesics, NSAIDs, and slow-acting antirheumatic drugs [SAARDs]) will be permitted to withdraw from the double-blind study drug. Subjects will either transition to open-label CZP treatment offered by UCB or to other treatment (including biologics) at the discretion of the Investigator until the assessment of the primary endpoint at Week 52. At the completion of the Week 52 visit assessments, subjects on double-

blind study treatment may receive open-label CZP treatment for an additional 2 years in an open-label, Safety Follow-Up Extension (SFE) Period. Subjects who withdrew from double-blind study treatment and transitioned to open-label CZP treatment are also eligible to participate in the SFE Period after completing the Week 52 visit assessments. Subjects on alternative treatments are not eligible to participate in the SFE Period.

All subjects not participating in the SFE Period after study completion at Week 52, including those withdrawn from the study prematurely, will have a FU visit 8 weeks after their Week 52 visit.

If the Investigator chooses to withdraw subjects on the other treatments (including biologics), the local guidelines on initiation and monitoring of the particular treatment should be followed.

The primary objective of the study is to demonstrate the efficacy of CZP administered at the dose of CZP 200mg Q2W, after a loading dose of CZP 400mg at Weeks 0, 2, and 4, on the signs and symptoms of active axSpA in subjects without x-ray evidence of AS.

The secondary objectives of the study are to assess efficacy, safety, and tolerability and to demonstrate the effect of CZP on health outcomes, disease activity, sacroiliac (SI) joint inflammation through MRI, and changes in concomitant and background medications.

Other objectives are to evaluate the effects of CZP on spinal mobility, total and nocturnal spinal pain (NRS), spinal inflammation, SI joint structural changes, treatment response over time, additional signs and symptoms of the disease, subject's health status, acute phase reactant (CRP), health-related quality of life (HRQoL), work and household productivity, pharmacokinetics (PK) and immunogenicity, gene and protein expression and to explore the relationship between genomic biomarkers and disease biology, drug treatment and inflammatory and immune responses (for those subjects who consent to the genomics substudy).

The primary efficacy variable is Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) response at Week 52. The secondary efficacy variables are ASAS 40% (ASAS40) response at Weeks 12 and 52, change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Weeks 12 and 52, change from Baseline in BASDAI at Weeks 12 and 52, change from Baseline in SI joint Spondyloarthritis Research Consortium of Canada (SPARCC) score at Week 12, the number of subjects without relevant changes to background medication, change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) at Week 52, change from Baseline in nocturnal spinal pain (NRS) at Week 52, and the number of subjects with anterior uveitis (AU) or new AU flares through Week 52.

For Canada (and any other country where applicable or where requested by Regulatory Authorities), the primary efficacy variable is the ASAS40 response at Week 12. The secondary efficacy variables are ASAS40 response at Week 52, ASDAS-MI at Week 52, change from Baseline in BASFI at Weeks 12 and 52, change from Baseline in BASDAI at Weeks 12 and 52, change from Baseline in SI joint SPARCC score at Week 12, the number of subjects without relevant changes to background medication, change from Baseline in ASQoL at Week 52, change from Baseline in nocturnal spinal pain (NRS) at Week 52, and the number of subjects with AU or new AU flares through Week 52.

Other efficacy variables are listed in Section 4.1.3.

Pharmacokinetic, exploratory biomarker, and pharmacogenomic variables are listed in Section 4.2 and immunogenicity variables are listed in Section 4.3.

Safety variables to be assessed are adverse events (AEs), vital signs, physical examination, and measurements of laboratory parameters. In addition, subjects will be evaluated at Screening, Baseline, and at every 12 weeks thereafter up to Week 36 and including Week 52/Withdrawal (WD) (for subjects not participating in the SFE Period) for signs and symptoms of latent or active tuberculosis (TB) infection and risk factors for exposure to TB using the TB questionnaire.

Approximately 1200 subjects will be screened in order to have 300 subjects (150 subjects per treatment group) randomized into the study. Randomization will be stratified by presence of sacroiliitis on MRI and elevated CRP to ensure balanced treatment allocation across 3 subgroups: MRI+/CRP+; MRI+/CRP-; MRI-/CRP+.

For each subject, the study will consist of 3 periods and will last a maximum of 66 weeks:

- Screening Period lasting up to 6 weeks
- Double-Blind, Placebo-Controlled Period for 52 weeks
- FU Period 8 weeks after the Week 52/WD visit (for subjects not participating in the SFE Period).

For subjects participating in the SFE Period, the study will extend up to a maximum of 104 additional weeks.

The estimated recruitment period is up to 15 months. The first subject first visit is planned in Quarter 3 2015. The end of the study will be defined as the date of the last subject's last visit, defined as the FU visit 8 weeks after the Week 52/WD visit for subjects not participating in the SFE Period, or the last visit of the SFE Period.

2 INTRODUCTION

2.1 Natural history of axial spondyloarthritis

Spondyloarthritis (SpA) is an umbrella term applied to a family of rheumatic diseases that have features in common with and distinct from other inflammatory arthritides, particularly rheumatoid arthritis (RA).

Recently, the ASAS working group established classification criteria to distinguish 2 broad categories of SpA: peripheral and axial SpA (axSpA) (Rudwaleit et al, 2011; Rudwaleit, 2010; Rudwaleit et al, 2009b). This division is based on the body part predominantly involved in the inflammatory process and those areas of the body that may respond similarly well to medication. Therefore, peripheral SpA includes diseases affecting mainly peripheral joints, such as reactive arthritis and psoriatic arthritis (PsA), whereas axSpA comprises those diseases with mainly axial involvement (SI joints and spine), including AS and nonradiographic axSpA (nr-axSpA).

Patients with AS have definitive evidence of structural changes in the SI joint (sacroiliitis) on x-ray, fulfilling the Modified New York classification criteria (mNY-positive) (van der Linden et al, 1984a), whereas those with nr-axSpA have no definitive structural changes on conventional radiographs (mNY-negative) (Rudwaleit et al, 2005; Dougados et al, 1991).

Axial SpA is a chronic inflammatory disease that impacts a substantial proportion of the population. Limited evidence exists regarding the exact prevalence of axSpA; however, recent data suggest that the prevalence is similar to that of RA in the United States of America (USA) (axSpA: 0.7% to 1.4%; RA: 0.5% to 1.0%) (Reveille et al, 2012; Myasoedova et al, 2010; Helmick et al, 2008).

The majority of patients with axSpA have inflammatory back pain. The disease typically originates in the SI joints, then progresses to the spine. In the SI joints and the spine, active inflammation results in erosions, sclerosis, and fatty lesions. However, the most characteristic feature is new bone formation leading to ankylosis of the SI joints and syndesmophytes attached to the vertebral bodies. As a result of extended syndesmophyte formation, the spine may become fused over time. Objective signs of inflammation, such as enthesitis, dactylitis, peripheral arthritis, or uveitis; genetic features, such as the presence of human leukocyte antigen B27 (HLA-B27); and laboratory parameters, such as elevated CRP, may also be present (Braun, 2012; Rudwaleit et al, 2009a; Braun and Sieper, 2007). Disability in axSpA is related to both the degree of inflammatory activity, causing pain, stiffness, fatigue, and poor quality of sleep, and to the degree of bony ankylosis, causing loss of spinal mobility.

The natural history of axSpA is characterized by a variable disease course. Over time, patients may develop structural damage or radiographic abnormalities involving their SI joints, and they may fulfill the mNY classification criteria for AS. However, the rate of development of structural damage varies among patients (Rudwaleit and Sieper, 2012). Some patients develop only unilateral sacroiliitis, and others may never develop definitive sacroiliitis on x-ray despite significant disease burden and other signs and symptoms of the disease, such as spinal lesions, uveitis, enthesitis, and peripheral arthritis. Approximately 10% of patients with nr-axSpA (25% if CRP levels are elevated) develop definitive evidence of sacroiliitis on x-ray within 2 years (Sieper and van der Heijde, 2013a).

2.2 Burden of disease in axSpA

Axial SpA typically presents in patients <45 years of age, and these relatively young and otherwise healthy patients face a significant disease burden regardless of whether or not they have definitive evidence of sacroiliitis on x-ray. These patients experience substantial pain, prolonged, severe stiffness of joints, substantial sleep disturbances, reduced mobility and overall function, reduced quality of life (QoL), loss of productivity, and other disease-related symptoms (Huscher et al, 2006; Kobelt et al, 2006; Kobelt et al, 2004; Boonen et al, 2003; Boonen et al, 2002; Ward, 2002). Moreover, studies have shown that the economic impact of the disease on society or patients can be substantial and that the costs are mainly driven by the cost associated with loss of work capacity (van der Heijde et al, 2013; Kobelt et al, 2006; Kobelt et al, 2004; Boonen et al, 2003; Ward, 2002).

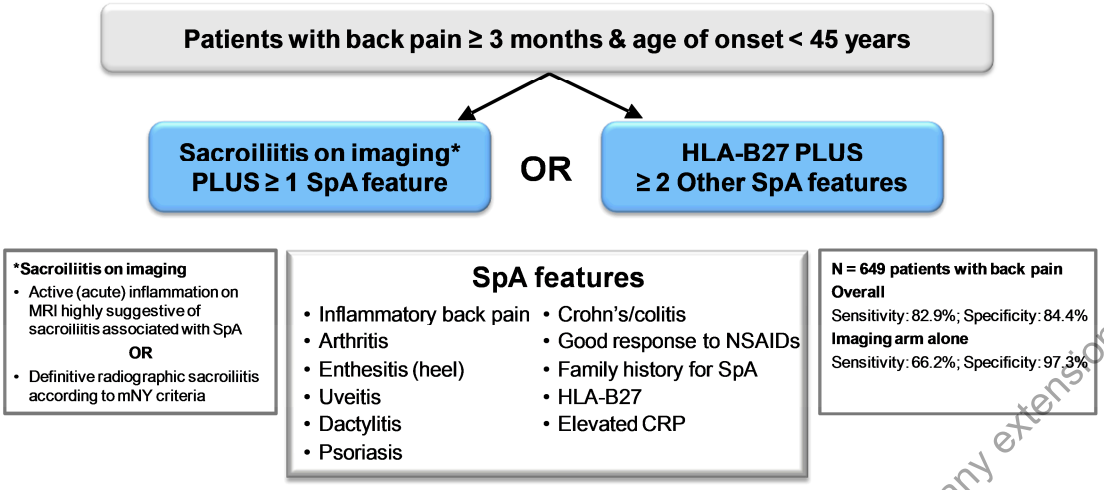
Several large observational and noninterventional cohort studies (Cuirea et al, 2013; Sieper and van der Heijde, 2013a) reported a similar burden of disease at study baseline across AS studies (captured through BASFI and BASDAI) in nonradiographic as well as radiographic axSpA (captured through BASDAI). A literature review of studies in both populations (Callhoff et al, 2015) and a recent study with CZP (RAPID-AxSpA) (Landewe et al, 2014) confirmed this finding in the clinical study setting.

2.3 Diagnosing axSpA in clinical practice

The diagnosis of AS and/or axSpA should be based on clinical assessments considering typical signs and symptoms, but also excluding other diseases that may have similar presentations. The mNY classification criteria, often used to support the diagnosis of AS, excludes patients who do not show definitive evidence of sacroiliitis on x-ray (Rostom et al, 2010). For a definitive classification of AS, the mNY classification criteria require radiographic evidence of sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3 to 4 unilaterally PLUS at least 1 of the following clinical criteria: low back pain and stiffness for ≥3 months, limitation of lumbar spine motion, or limitation of chest expansion. These criteria were designed for classification of patients in clinical trials rather than for diagnostic purposes. However, they have historically been used for clinical diagnosis. The requirement for limitations in spinal motion and/or chest expansion has led to diagnoses being delayed until irreversible structural damage is documented on SI joint x-rays. Several publications have documented that time from symptom onset until the diagnosis of AS ranges from 5 years to 10 years (van der Linden et al, 1984b; Feldtkeller et al, 2003; Feldtkeller et al, 2000), thus demonstrating that x-ray changes lag far behind other signs and symptoms.

Due to the problem of delayed disease recognition, ASAS developed new classification criteria for axSpA that do not require the presence of definitive sacroiliitis on x-ray, thus identifying a nonradiographic subpopulation (nr-axSpA) allowing for classification of all axSpA patients (Rudwaleit et al, 2009b; Rudwaleit et al, 2009c). These criteria establish standards that apply to patients with or without radiographic sacroiliitis enabling the conduct of clinical trials in patients with both nr-axSpA and AS. In patients with a history of chronic back pain for ≥3 months and age of onset <45 years, classification of axSpA can be made based on either evidence of sacroiliitis on radiographs or MRI plus ≥1 typical SpA feature or the presence of HLA-B27 plus ≥2 typical SpA features (Figure 2–1). In these criteria, sacroiliitis is defined as MRI evidence of SI joint inflammation or radiographic evidence of sacroiliitis meeting mNY criteria (Rostom et al, 2010).

Figure 2–1: ASAS Classification Criteria for axSpA



ASAS=Assessment of SpondyloArthritis International Society; axSpA=axial spondyloarthritis; CRP=C-reactive protein; HLA-B27=human leukocyte antigen B27; mNY=modified New York; MRI=magnetic resonance imaging; NSAID=nonsteroidal anti-inflammatory drug; SpA=spondyloarthritis. Adapted from Rudwaleit M, et al. Ann Rheum Dis. 2009; 68(6):777-783 (Rudwaleit et al, 2009c).

2.4 Current management of axial spondyloarthritis

There is increasing recognition of axSpA as an important clinical entity, as evidenced by the efforts of the American College of Rheumatology (ACR) in cooperation with the Spondylitis Association of America (SAA) and the Spondyloarthritis Research and Treatment Network (SPARTAN) to develop new treatment recommendations for axSpA including AS (see Appendix 18.1 for classification criteria for axSpA). To help Investigators and at the same time reduce the introduction of bias in the study resulting from changes in background medications, UCB is recommending allowed changes in background therapy. These allowed changes were prepared by expert rheumatologists from North America and Europe and have also been aligned with the draft ACR/SAA/SPARTAN Recommendations for the Management of Axial Spondyloarthritis, including Ankylosing Spondylitis, and Children with the Enthesitis-Related Arthritis Form of Juvenile Idiopathic Arthritis presented at the recent ACR Nov 2014 meeting in Boston. Furthermore, the update of the 2006 ASAS recommendations for the use of anti-tumor necrosis factor (TNFs) for AS extended the recommendations to patients fulfilling the ASAS criteria, including patients with nr-axSpA (van der Heijde et al, 2011).

Nonsteroidal anti-inflammatory drugs are often rapidly effective for the symptoms (pain and stiffness) of axSpA (Poddubnyy, 2013; Poddubnyy et al, 2012), but many patients lose symptomatic response and structural damage often progresses despite their use. Conventional disease-modifying antirheumatic drugs (DMARDs; eg, methotrexate [MTX] and sulfasalazine [SSZ]) have limited efficacy in axial disease, but may benefit patients with peripheral joint disease (Haibel et al, 2007; Braun et al, 2006; Haibel et al, 2005). Therefore, DMARDs are recommended only in patients with predominantly peripheral manifestations (Braun and van den Berg, 2011).

Patients who are intolerant of or have inadequately responded to NSAIDs, or those in whom NSAIDs are contraindicated, have limited treatment options. Tumor necrosis factor-alpha inhibitors (TNFi) (CZP, adalimumab [ADA] etanercept [ETN] infliximab [IFX]), golimumab

[GOL]) are the only effective and approved treatment options as of Dec 2014; IFX and GOL are indicated for active AS only, while CZP, ADA, and ETN are indicated for axSpA without radiographic evidence of AS (nr-axSpA) as an addition to the AS indication in several regions.

At the 2014 Annual Meeting of the ACR/SPARTAN group a draft treatment guideline was presented for the subject suffering from both AS and nr-axSpA. These guidelines recommend the use of a TNFi after NSAID treatment.

With the advent of the ASAS classification criteria for axSpA, several registration studies have been conducted in patients with nr-axSpA (Dougados et al, 2014), or axSpA (Landewe et al, 2014; Sieper et al, 2013b; Sieper et al, 2013c). These studies have shown that anti-TNFs are effective in nr-axSpA patients, particularly in patients with objective signs of inflammation as defined by MRI positivity or elevated CRP. The RAPID-axSpA study, the first axSpA study to enroll both AS and nr-axSpA patients in the same study, showed that baseline disease activity and treatment effect were similar between nr-axSpA and AS subjects (Landewe et al, 2014). In this study, it was shown that CZP rapidly reduced the signs and symptoms of axSpA disease over 24 weeks of Double-Blind treatment in the broad axSpA population, including the AS and the nr-axSpA subpopulations, and that the responses to the treatment were similar in both subpopulations (Landewe et al, 2014; Sieper and van der Heijde, 2013c) and maintained up to Week 96 (Mease et al, 2014; Sieper et al, 2014).

Based on the results of the RAPID-axSpA study, CZP received approval for the treatment of adult patients with severe active axSpA (comprising AS and nr-axSpA) in the European Union (EU) and several other countries, eg, Turkey, Argentina, Russia, Chile, Switzerland, Hong Kong, Dominican Republic, Ecuador, and Peru, and it was approved for the treatment of adults with active AS in the USA, Canada, Australia, and also Malaysia.

In accordance with the ASAS classification criteria a subject can either be classified as having axSpA based on imaging evidence or on clinical assessment. Recent publications showed that sacroiliitis on imaging via MRI is highly specific for the diagnosis of axSpA and is commonly used in many regions to diagnose axSpA in daily clinical practice (Rudwaleit et al, 2009a; Rudwaleit et al, 2009b; Rudwaleit et al, 2009c).

Because of the therapeutic response in early disease, the ASAS consensus recommendation on the use of TNFi in AS, updated in 2010, was extended to include the full spectrum of axSpA (van der Heijde et al, 2011).

2.5 Rationale

The RAPID-axSpA study enrolled subjects with objective signs of inflammation, and the results indicated that baseline disease burden was similar between the AS and nr-axSpA subpopulations (Landewe et al, 2014; Sieper et al, 2013b). In the RAPID-AxSpA study it was shown that CZP rapidly reduced the signs and symptoms of axSpA over 24 weeks of double-blind treatment in the broad axSpA population, including in the AS and the nr-axSpA subpopulations, and that the responses to the treatment were similar in both subpopulations (Landewe et al, 2014; Sieper et al, 2013b) and maintained up to Week 96 (Mease et al, 2014; Sieper et al, 2014).

To address the unmet need for treatment options for nr-axSpA, AS0006 will be conducted focusing on subjects who do not meet the mNY classification criteria for AS (see Appendix 18.2). Data suggest that patients with objective signs of inflammation and high

disease activity are likely to run a chronic disease course and unlikely to be well-managed on conventional therapy (Rudwaleit ACR, 2013). Furthermore, studies where anti-TNFs have been withdrawn in nr-axSpA patients show that patients flare quickly and hence the disease is unlikely to go into spontaneous remission. However, there are no long-term prospective studies to assess how patients meeting the ASAS classification criteria respond to conventional therapies. With the conduct of the 52-week blinded study period comparing CZP to placebo in combination with standard of care, a better understanding should be gained of how a long-term anti-TNF therapy compares to standard of care in patients meeting the ASAS criteria with objective signs of inflammation. Moreover, patients whose disease cannot be managed under the blinded study treatment conditions will be able to discontinue the double-blind study treatment and transition to either open-label CZP or other therapies.

The addition of the SFE Period will allow collection of long-term safety data from eligible subjects on open-label CZP for up to 2 years. During the SFE Period, CZP will be provided by the Sponsor. The treating investigator is requested to apply routine, standard of care according to local standard medical practice and investigator clinical judgment.

Subjects enrolled into this study must have sacroiliitis on MRI as set forth by the ASAS/OMERACT definition; or meet the requirements for the clinical arm of the ASAS classification criteria for axSpA (MRI-negative nr-axSpA) and have elevated CRP levels, as there is good evidence to suggest that CRP is a predictor of response to anti-TNF therapy in axSpA.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of the study is to demonstrate the efficacy of CZP 200mg Q2W on the signs and symptoms of subjects with active axSpA without x-ray evidence of AS.

3.2 Secondary objectives

The secondary objectives of the study are to assess efficacy, safety, and tolerability and to demonstrate the effect of CZP on:

- Health outcomes
- Disease activity
- SI joint inflammation through MRI
- Changes in concomitant and background medications

3.3 Other objectives

The other objectives of the study are to assess the effect of CZP on the following:

- Spinal mobility
- Total spinal pain (NRS)
- Spinal inflammation
- SI joint structural changes

- Treatment response over time
- Additional signs and symptoms of the disease
  - Morning stiffness
  - Fatigue
  - Extra-articular manifestations of axSpA
  - Sleep
  - Physical function
- Subject's health status
- Acute phase reactant (CRP)
- HRQoL
- Work and household productivity
- PK and immunogenicity
- Gene and protein expression and to explore the relationship between genomic biomarkers and disease biology, drug treatment and inflammatory and immune responses (for those subjects who consent to the genomics substudy).

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variable

- ASDAS-MI at Week 52

The primary efficacy variable for Canada (and any other country where applicable or where requested by Regulatory Authorities) is the ASAS40 response at Week 12.

4.1.2 Secondary efficacy variables

The secondary efficacy variables are as follows:

- ASAS40 response at Weeks 12 and 52
- Change from Baseline in BASFI at Weeks 12 and 52
- Change from Baseline in BASDAI at Weeks 12 and 52
- Change from Baseline in SI joint SPARCC score at Week 12
- Number of subjects without relevant changes to background medication
- Change from Baseline in ASQoL at Week 52
- Change from Baseline in ASQoL at timepoints other than Week 52
- Change from Baseline in nocturnal spinal pain (NRS) at Week 52
- Number of subjects with AU or new AU flares through Week 52

For Canada (and any other country where applicable or where requested by Regulatory Authorities), the secondary efficacy variables are:

- ASAS40 response at Week 52
- ASDAS-MI at Week 52
- Change from Baseline in BASFI at Weeks 12 and 52
- Change from Baseline in BASDAI at Weeks 12 and 52
- Change from Baseline in SI joint SPARCC score at Week 12
- Number of subjects without relevant changes to background medication
- Change from Baseline in ASQoL at Week 52
- Change from Baseline in ASQoL at timepoints other than Week 52
- Change from Baseline in nocturnal spinal pain (NRS) at Week 52
- Number of subjects with AU or new AU flares through Week 52

4.1.3 Other efficacy variables

The following variables will be analyzed at scheduled time points through Week 52:

- ASAS 20% response criteria (ASAS20), ASAS40, ASAS 20% improvement in 5 of 6 domains (ASAS5/6), and ASAS partial remission response
- Change from Baseline in individual ASAS components:
  - Patient's Global Assessment of Disease Activity (PGADA)
  - Total spinal pain (NRS)
  - BASFI
  - Average of Questions 5 and 6 of the BASDAI concerning morning stiffness
  - Change from Baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) lateral spine flexion
  - CRP
- Change from Baseline in BASDAI and individual Questions 1, 2, 3, and 4
- Change from Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS)
- Change from BASMI linear
- ASDAS disease activity (Ankylosing Spondylitis Disease Activity Score inactive disease [ASDAS-ID], Ankylosing Spondylitis Disease Activity Score moderate disease [ASDAS-MD], Ankylosing Spondylitis Disease Activity Score high disease activity [ASDAS-HD], Ankylosing Spondylitis Disease Activity Score very high disease activity [ASDAS-vHD]) and clinical improvement (Ankylosing Spondylitis Disease Activity Score clinically important improvement [ASDAS-CII], ASDAS-MI)
- BASDAI 50 response

- Change from Baseline in Fatigue (NRS) (from BASDAI)
- Change from Baseline in sacroiliitis grading to Week 52 for structural damage
- Change from Baseline in SI joint SPARCC score at Week 52 and ankylosing spine MRI acuity (ASspiMRI-a) in the Berlin modification at Week 12 and Week 52
- Proportion of subjects with SI joint SPARCC score <2 at Week 12 and Week 52
- Change from Baseline in ASAS-NSAID score
- Number of AU flares
- Number of inflammatory bowel disease (IBD) exacerbations
- Number of psoriasis exacerbations
- Work Productivity Survey (WPS)
- Change from Baseline in the Sleep Problems Index II domains of the Medical Outcomes Study (MOS) Sleep scale
- Change from Baseline in enthesitis (Maastricht Ankylosis Spondylitis Enthesitis Score [MASES])
- Change from Baseline in swollen and tender joint counts (44 joint count)
- Change from Baseline in Physician's Global Assessment of Disease Activity (PhGADA)
- Change from Baseline in the Short-Form 36-Item Health Survey (SF-36), Physical Component Summary (PCS), and Mental Component Summary (MCS)
- Change from Baseline in the SF-36 domains:
  - Role Physical
  - Bodily Pain
  - General Health
  - Vitality
  - Social Functioning
  - Role Emotional
  - Mental Health
- Health status as assessed by the EuroQoL Health Status Questionnaire (5 dimensions) (EQ-5D) domains, visual analog scale (VAS) actual score and change from Baseline in VAS score
- Resources utilization: concomitant medical procedures, health care provider consultations not foreseen by the protocol, hospitalizations/emergency room visits

4.2 Pharmacokinetic, exploratory biomarker, and pharmacogenomic variables

4.2.1 Primary pharmacokinetic variables

Certolizumab pegol plasma concentrations will be measured at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52, and at the FU visit (8 weeks after the Week 52/WD visit).

These plasma samples may be used additionally for analyses of CZP and its constituent moieties using alternative methods.

4.2.2 Exploratory biomarkers variables

Selected samples collected for measurement of CZP plasma concentration may be used additionally for analyses of candidate exploratory biomarkers and cytokines, where appropriate. The biomarkers to be analyzed may include, but will not be limited to the following:

Matrix metalloproteinase-3 (MMP-3), bone morphogenetic protein (BMP)-2, -4 and -7, wingless-related mouse mammary tumor virus integration site protein (WNT1), WNT1-inducible signaling pathway proteins (WISP), gremlin, dickkopf-related protein 1 (DKK1), sclerostin, hedgehog proteins (Sonic hedgehog [Shh], Indian hedgehog [Ihh], Dessert hedgehog [Dhh]), collagen turnover/cleavage products, collagen type X, vascular endothelial growth factor (VEGF), citrullinated vimentin fragments, cytokines: interleukin 13 (IL13), interleukin 17A and F (IL17 A and IL17 F), interleukin 23 (IL23), interleukin 34 (IL34), transforming growth factor (TGF) β, macrophage colony-stimulating factors (M-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), colony-stimulating factor-1 (CSF-1), and soluble CSF-1 receptor (sCSF1r) levels.

4.2.3 Pharmacogenomic variables

For individuals consenting to the genomics substudy, blood samples will be drawn for possible genetic/epigenetic, genomic, proteomic, and metabolomics analysis at Baseline and Week 12. Additional samples will be collected for genomics, proteomics, and metabolomics analysis only, at Weeks 4 and 52/WD.

Collection of the samples will enable the exploratory evaluation of biomarkers relative to disease activity, drug treatment, and inflammatory and immune response processes. The nature and format of these tentative analyses will be determined when the results of the main study are made available. The samples will be stored at -80°C at the central biorepository for up to 20 years.

4.3 Immunological variables

Anti-CZP antibody/anti-drug antibody (anti-CZP Ab/ADAb) concentrations will be assessed at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52/WD, and the FU visit (8 weeks after the Week 52/WD visit). In addition, the anti-CZP Ab concentrations will be assessed in subjects who withdraw from study drug and transition to open-label CZP.

Determination of ADAb will be done using a validated screening, confirmation and titration ADAb bridging assay, with potential further characterization by a neutralizing antibody assay. The immunogenicity data will be processed according to dedicated Bioanalytical Analysis plans.

4.4 Safety variables

Safety variables to be assessed are physical examinations, AEs, vital signs, and measurements of laboratory parameters.

Adverse events will be solicited at every visit, and recorded and coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA®) criteria.

Physical examination findings will be recorded in the case report form (CRF) only at Screening. Clinically important abnormal changes in subsequent physical examinations will be recorded as AEs at all visits from Baseline to the FU visit.

Clinical laboratory values (hematology, biochemistry, urinalysis) will be collected and assessed at Screening, Baseline, Weeks 2, 4, 8, 12, 24, 36, at the end of study completion at Week 52/WD visit and at the FU visit (8 weeks after the Week 52/WD visit). In addition, clinical laboratory values will be collected and assessed at study visits during the administration of open-label CZP in subjects who withdraw from the double-blind study treatment.

Furthermore, CRP will be collected and assessed either in a blinded or open manner at Screening, 3 to 5 days before Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and at the end of study completion at Week 52/WD visit and at the FU visit (8 weeks after the Week 52/WD visit).

At Screening, all subjects will have an Interferon-Gamma Release Assay (IGRA) test (QuantiFERON® TB test or Elispot® test, when the QuantiFERON test indicated is not available), and a chest x-ray reading (or, if done, computed tomography of the chest) which must be reported consistent with standard clinical reporting practice by an experienced qualified TB specialist, radiologist, or a pulmonologist, who is specifically required to look for signs of active TB or signs of past/inactive TB infection. A chest x-ray will not be done at Screening if a chest x-ray (or computed tomography of the chest) was done within 3 months prior to the Screening visit. The official report of the imaging must specifically indicate the absence of findings suggestive of current active TB or prior inactive TB. In addition to a physical examination done intermittently throughout the study, subjects will be evaluated at Screening, Baseline, and every 12 weeks thereafter up to Week 36 and including the Week 52/WD visit, for signs and symptoms of latent tuberculosis (LTB) or active TB infection and risk factors for exposure to TB using the TB questionnaire.

5 STUDY DESIGN

5.1 Study description

Study AS0006 is a 52-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study to evaluate the efficacy and safety of CZP in adult subjects with active axSpA without x-ray evidence of AS and with objective signs of inflammation (sacroiliitis on MRI and/or elevated CRP) and who have had an inadequate response to, have a contraindication to, or are intolerant to NSAIDs. At the completion of the Week 52 visit assessments, eligible subjects may receive open-label CZP treatment for an additional 2 years in an open-label, SFE Period.

5.1.1 Study periods

The study includes 3 periods. An injection schedule is provided in Section 7.2.2.

Period 1 (Screening Period): 1 day to 6 weeks before Baseline:

Prior to any study activities, subjects will be asked to read and sign the Informed Consent form for the conduct of the study. A separate informed consent form will also be obtained from subjects consenting to the use of their blood samples in a substudy for possible genetic/epigenetic, genomic, proteomic, and metabolite analysis.

Laboratory data (hematology, urine, and biochemistry tests) will be obtained, and treatment of LTB will be initiated when necessary. Subjects must undergo a TB test and complete a TB questionnaire. The BASDAI, BASMI, and spinal mobility assessments will be performed. Concomitant medications permitted during the study should remain stable for at least 4 weeks prior to Baseline at Week 0.

Sacroiliac-joint x-ray (not older than 12 months before Baseline and verified by central reading during the Screening Period) must prove that the subject belongs to the mNY-negative axSpA subpopulation, ie, does not have sacroiliitis grade ≥2 bilaterally or grade 3 to 4 unilaterally. Potentially eligible axSpA subjects without suitable SI-joint x-ray must undergo the x-ray with central reading within the Screening Period. Sacroiliac-joint x-rays (read centrally) will allow discrimination of subjects with AS and without definitive evidence for sacroiliitis on x-ray (mNY negative-axSpA). Subjects with AS (mNY-positive) must be excluded from further participation in this study.

Confirmed mNY-negative axSpA subjects must undergo an MRI later during the Screening Period for central reading with results from the central reading available by no later than at the Baseline visit.

Additionally, the subjects must get a further measurement of CRP 3 to 5 days before Baseline (Week 0).

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

Eligible subjects will be allocated to the following double-blind study treatments in a 1:1 ratio:

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

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site. At the Week 0, 2, 4, 6, and 8 visits, the administration must be done by dedicated, unblinded, and adequately trained site personnel. At the Week 10 and 12 visits, the subject will receive training on self-injection and the study treatment will be self-administered under the supervision of the unblinded study personnel. At Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50, the study treatment administration should preferably be done by the unblinded study personnel, or alternatively by self-injection of the subject under the supervision of the unblinded study personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. Concomitant medications permitted during the study should remain stable for at least 4 weeks prior to the Weeks 12, 24, and 52/WD assessments.

Alternative schedules

Subjects who discontinue the double-blind study treatment and enter open-label treatment with CZP will be assessed 2 and 4 weeks after open-label CZP treatment has been initiated and every 12 weeks thereafter. Alternatively, subjects who discontinue the double-blind study treatment and receive other treatment (including biologics) will be assessed every 12 weeks after initiation of the other treatment. The alternative schedules for open-label CZP and other treatment can be found in Table 5–2 and Table 5–3, respectively. In either alternative schedule, assessments should be conducted until as close as possible to Week 52 (within ±4 weeks), where Week 52 is relative to the original randomization at Week 0. Subjects will then be invited to the Week 52 assessment visit.

Period 3 (Follow-Up Period):

All subjects not participating in the SFE Period after Week 52, including those withdrawn from the study prematurely, will have a FU visit 8 weeks after the Week 52/WD visit.

Safety Follow-Up Extension (SFE) Period: Week 52 to Week 156, open-label.

At the completion of the Week 52 visit assessments, subjects on double-blind study treatment may receive open-label CZP treatment for an additional 2 years. Subjects who withdrew from double-blind study treatment and transitioned to open-label CZP treatment are also eligible to participate in the SFE Period after completing the Week 52 visit assessments. Subjects on alternative treatments are not eligible to participate in the SFE Period.

Eligible subjects are allowed to roll-over to the SFE Period up to 3 months after completion of the Week 52 assessments.

In order to maintain the blind for subjects completing double-blind treatment, their study treatment will be administered sc at the study site by unblinded, dedicated study personnel on Weeks 52, 54, and 56. Subjects who withdrew from double-blind study treatment and transitioned to open-label CZP treatment do not need to visit the site at Week 54 and Week 56, and should continue their open-label CZP treatment regimen.

For the remainder of the SFE Period, CZP can be administered at the site by dedicated study personnel, or by self-injection of the subject under the supervision of the dedicated study personnel, or subjects may self-administer their study treatment Q2W at home.

Starting at Week 64, all subjects are to visit the site approximately every 12 weeks for assessments.

The last dosing visit will be at Week 154. The final study assessments are performed at Week 156.

5.1.2 Study duration per subject

For each subject, the first 3 periods of the study will last a maximum of 66 weeks, as follows:

- Up to 6 weeks in the Screening Period
- 52 weeks in the Double-Blind Period
- A FU visit 8 weeks after the Week 52/WD visit (for subjects not participating in the SFE Period).

For subjects participating in the SFE Period, the study will extend up to a maximum of 104 additional weeks.

The estimated recruitment period is up to 15 months. The first subject first visit is planned in Quarter 3 of 2015. The end of the study will be defined as the date of the last subject's last visit, defined as the FU visit 8 weeks after the Week 52/WD visit for subjects not participating in the SFE Period, or the last visit of the SFE Period

5.1.3 Planned number of subjects and site(s)

Approximately 1200 subjects are expected to enter the Screening Period in order to have 300 subjects randomized into the Double-Blind Period. The end of the study will be defined as the date of last subject last FU visit. It is planned to enroll the subjects at approximately 120 sites.

5.1.4 Anticipated regions and countries

The study will be conducted in North America, Australia, Europe, Asia, and other regions as appropriate.

5.2 Schedule of study assessments

The Schedule of assessments is shown in Table 5–1 for subjects who complete 52 weeks of treatment on either CZP 200mg Q2W or placebo.

In order to optimize the treatment the Investigator may adjust the background medication in accordance with the specifications described in Table 7–1.

At any time during the study course, but preferably not before Week 12, the Investigator may discontinue the double-blind study treatment and start open-label treatment with either CZP (which will be provided free of charge by UCB) or an alternative drug (eg, other treatment [including biologics]). Table 5–2 shows the schedule of assessments for subjects receiving open-label treatment with CZP and Table 5–3 shows the schedule of assessments for subjects receiving an alternative treatment (not CZP).

Table 5–6 shows the schedule of assessments for subjects participating in the SFE Period.

Table 5–1: Schedule of study assessments – Screening through Week 52 and FU

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

Table 5–1: Schedule of study assessments – Screening through Week 52 and FU

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

Table 5–1: Schedule of study assessments – Screening through Week 52 and FU

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

Abs=antibodies; AE=adverse event; Apo=Apolipoprotein; AsQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; axSpA=axial spondyloarthritis; BASMI=Bath Ankylosing Spondylitis Metrology Index;

Table 5–1: Schedule of study assessments – Screening through Week 52 and FU

Visit #	Scr	Scr day -5 to -3	1/BL	2	3	4	5	6	7	8	9H	10	11H	12	13H	14	15H	16	17H	18	19H	20	21H	22	23H	24	25H	26	27	28	
Week **Protocol Activity**	**-6 weeks to -1 day**		**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14/H**	**16**	**18/H**	**20**	**22/H**	**24**	**26/H**	**28**	**30/H**	**32**	**34/H**	**36**	**38/H**	**40**	**42/H**	**44**	**46/H**	**48**	**50**	**52/WD**	**FU**[b]

BL=Baseline; CKD-EPI=Chronic Kidney Epidemiology Collaboration; CRP=C-reactive protein; CZP=certolizumab pegol; EQ-5D=EuroQoL Health Status Questionnaire (5 dimensions); FU=Follow-Up; H=home; HbA1c=glycated hemoglobin; HBsAg=Hepatitis B surface antigen; HIV=human immunodeficiency virus; HLA-B27=Human Leukocyte Antigen-B27; IGRA=Interferon-Gamma Release Assay; IXRS=Interactive Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MOS=Medical Outcomes Study; MRI=magnetic resonance imaging; PE=physical exam; PhGADA=Physician's Global Assessment of Disease Activity; PGADA=Patient's Global Assessment of Disease Activity; sc=subcutaneously; Scr=Screening; SF-36=Short-Form 36-item Health Survey; SFE=safety Follow-up Extension; SI=sacroiliac; TB=tuberculosis; WD=Withdrawal

Note: All weeks are ±3 days compared to Baseline.

Note: At the completion of the Week 52 visit, subjects may receive open-label CZP treatment for an additional 2 years in the SFE Period

[a] Informed consent: Prior to any study activities, subjects will be asked to read and sign the informed consent form for the conduct of the study. A separate informed consent form will also be obtained from subjects consenting to the use of their blood samples in a substudy for possible genetic/epigenetic, genomic, proteomic, and metabolite analysis.

[b] FU: 8 weeks after Week 52/WD visit for subjects not participating in the SFE Period.

[c] Pulse rate, systolic and diastolic blood pressures, temperature, and respiration rate are to be measured at Screening and Baseline, thereafter pulse rate, systolic and diastolic blood pressures, temperature are to be measured at all on-site visits. If a subject experiences an AE, respiration rate will be measured in addition.

[d] Subjects will be encouraged to be in fasting condition at Baseline and at Week 52/WD or at the time the subject shifts to alternative treatment, for Apo A1, ApoB, and lipoprotein(a) assessments.

[e] HbA1c will be measured at Baseline and Week 52/WD.

[f] Testing to rule out HBsAg, antibodies to hepatitis C, and HIV will be performed. In addition, testing for HLA-B27 and abnormalities for estimated glomerular filtration rate as measured by CKD-EPI are to be performed.

[g] One retest of CRP is mandatory during the Screening Period within 3 to 5 days before the Baseline visit in order to meet the inclusion criteria.

[h] Pregnancy testing must be carried out for women of childbearing potential: A serum test will be performed at the Screening visit and FU, and urine testing (dipstick) at Baseline and Week 52/WD.

[i] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Weight is to be measured at Screening, Week 24, and at completion at Week 52/WD. Height will be measured at the Baseline visit only.

[j] A chest x-ray must be done at Screening unless a chest x-ray (or computed tomography of the chest) has been done within 3 months prior to the Screening visit. The chest x-ray will be repeated at Week 52/WD visit only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure).

[k] TB test: IGRA test (QuantiFERON test [or Elispot test when the QuantiFERON indicated is not available]). The TB test will be repeated at Week 52 (or at WD visit if medically indicated) for subjects with previously negative TB test result. Subjects who tested positive for TB should be encouraged to complete a FU visit (8 weeks after the Week 52/WD visit for subjects not participating in the SFE Period) and follow-up information of suspected and confirmed TB cases

Table 5–1: Schedule of study assessments – Screening through Week 52 and FU

Visit #	Scr	Scr day -5 to -3	1/BL	2	3	4	5	6	7	8	9H	10	11H	12	13H	14	15H	16	17H	18	19H	20	21H	22	23H	24	25H	26	27	28	
Week **Protocol Activity**	**-6 weeks to -1 day**		**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14/H**	**16**	**18/H**	**20**	**22/H**	**24**	**26/H**	**28**	**30/H**	**32**	**34/H**	**36**	**38/H**	**40**	**42/H**	**44**	**46/H**	**48**	**50**	**52/WD**	**FU[b]**

should be provided to UCB at least after 3, 9, and 12 months of the start date of anti-TB treatment.

[l] Sacroiliac joint x-rays will be performed at Screening and Week 52/WD for all subjects. An SI joint x-ray will be performed ≤12 months prior to the Baseline visit.

[m] Magnetic resonance imaging of the spine and SI joints to be performed at Screening and at the Week 12 and at the Week 52/WD visits if MRI was performed more than 12 weeks prior to WD visit.

[n] Occiput to wall distance; chest expansion; and BASMI, which includes modified Schober test, lateral spinal flexion, cervical rotation, tragus to wall distance, and maximal intermalleolar distance.

[o] Resource utilization includes: concomitant medical procedures, health care provider consultations not foreseen by the protocol, hospitalizations/emergency room visits.

[p] Contact IXRS to register the visit and obtain next kit number, where applicable.

[q] At on-site visit days (Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site. At the Week 0, 2, 4, 6, and 8 visits, the administration must be done by dedicated, unblinded, and adequately trained site personnel. At the Week 10 and 12 visits, the subject will receive training on self-injection and the study treatment will be self-administered under the supervision of the unblinded study personnel. At Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50, the study treatment administration should preferably be done by the unblinded study personnel, or alternatively by self-injection of the subject under the supervision of the unblinded study personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. From Week 52 onwards, after completion of all onsite assessments and procedures, the subject may receive open-label CZP at the discretion of the Investigator.

[r] All subjects will receive training for self-injection at the study site on Weeks 10 and 12. During the training at the Weeks 10 and 12 visits, the double-blind study treatment will be self-administered under the supervision of the unblinded study personnel.

Table 5–2: Schedule of alternative study assessment with CZP - after subject discontinuation of the double-blind study treatment

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

Table 5–2: Schedule of alternative study assessment with CZP - after subject discontinuation of the double-blind study treatment

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

Table 5–2: Schedule of alternative study assessment with CZP - after subject discontinuation of the double-blind study treatment

Visit #	1 wdt	2 wdt	3 wdt				4 wdt						5 wdt			
Week **Protocol Activity**	**0**	**2**	**4**	**6H**	**8H**	**10H**	**12**	**14H**	**16H**	**18H**	**20H**	**22H**	**24 and Q12W**		**52/WD**	**FU[a]**

Abs=antibodies; AE=adverse event; AS=ankylosing spondylitis; AsQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CRP=C‑reactive protein; CZP=certolizumab pegol; EQ-5D=EuroQoL Health Status Questionnaire (5 dimensions); FU= Follow-Up; H=home, no site visit; HbA1c=glycated hemoglobin; IGRA=Interferon-Gamma Release Assay; IXRS=Interactive Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MOS=Medical Outcomes Study; PE=physical exam; Q2W=every 2 weeks; Q12W=every 12 weeks; sc=subcutaneously; SF‑36=Short‑Form 36‑item Health Survey; SFE=Safety Follow-up Extension; W=Week; WD=Withdrawal; wdt=withdrawal treatment

Note: If a subject switches from open-label CZP to other treatment (including biologics), the subject must follow the assessment schedule (Table 5–3) for other treatment (including biologics)

Note: All weeks are ±3 days compared to Baseline. Week 0 of the alternative schedule starts 2 weeks after the last dose of the double-blind study treatment.

Note: At the completion of the Week 52 visit, subjects who transitioned to open-label CZP treatment after withdrawal from the Double-Blind Period are eligible to participate in the SFE Period.

[a] FU: 8 weeks after Week 52/WD visit for subjects not participating in the SFE Period.

[b] Pulse rate, systolic and diastolic blood pressures, temperature, and respiration rate are to be measured at wdt Week 0 thereafter pulse rate, systolic and diastolic blood pressures, temperature are to be measured at all on-site visits. If a subject experiences an AE, respiration rate will be measured in addition.

[c] Subjects will be encouraged to be in fasting condition at the time the subject shifts to alternative treatment, for Apo A1, ApoB, and lipoprotein(a) assessments.

[d] HbA1c will be measured at wdt Week 0 and Week 52/WD.

[e] Pregnancy testing must be carried out for women of childbearing potential and will be a serum test at the FU visit and a urine test (dipstick) at wdt Week 0 (prior to initiation of open-label CZP) and Week 52/WD visit.

[f] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Weight is to be measured at wdt Week 0, Week 24, and at completion at Week 52/WD.

[g] If the last Q12W assessment for a subject who discontinues study treatment is ≤4 weeks before the final assessments visit at Week 52/WD, the assessment should be cancelled and the subject should instead be invited to undergo the final assessments visit at Week 52 (the Week 52/WD visit is to be scheduled 52 weeks [±3 days] after Baseline).

[h] TB test: IGRA test (QuantiFERON test [or Elispot test when the QuantiFERON test is indicated but not available]). The TB test will be repeated at Week 52 (or at WD visit if medically indicated) for subjects with previously negative TB test result.

[i] Occiput to wall distance; chest expansion; and BASMI, which includes modified Schober test, lateral spinal flexion, cervical rotation, tragus to wall distance, and maximal intermalleolar distance.

[j] A separate informed consent will be obtained prior to gene expression and proteomic assessments, if applicable.

[k] A telephone contact will be made with the subject every 4 weeks after the on-site visit (ie, at Weeks 8H, 16H, 22H, and every 4 weeks after Week 24 until Week 52/WD visit).

Table 5–2: Schedule of alternative study assessment with CZP - after subject discontinuation of the double-blind study treatment

Visit #	1 wdt	2 wdt	3 wdt				4 wdt						5 wdt			
Week **Protocol Activity**	**0**	**2**	**4**	**6H**	**8H**	**10H**	**12**	**14H**	**16H**	**18H**	**20H**	**22H**	**24 and Q12W**		**52/WD**	**FU[a]**

[l] Loading dose of CZP 400mg at Weeks 0, 2, and 4 must be administered by dedicated site staff.
[m] CZP administration will be continued Q2W.

Table 5–3: Schedule of alternative study assessment with other treatment (including biologics) - after subject discontinuation of the double-blind study treatment

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

Table 5–3: Schedule of alternative study assessment with other treatment (including biologics) - after subject discontinuation of the double-blind study treatment

Visit #	1 wdt	2 wdt	3 wdt			
Week **Protocol Activity**	**0**	**12**	**24 and Q12W**	**Continue W24 assess**	**52/WD**	**FU[a]**

Abs=antibodies; AE=adverse event; Abs=antibodies; AE=adverse event; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; CRP=C‑reactive protein; CZP=certolizumab pegol; eCRF=electronic case report form; FU= Follow-Up; H=home, no site visit; IXRS=Interactive Response System; PE=physical exam; Q12W=every 12 weeks; W=Week; WD=Withdrawal, wdt=withdrawal treatment
Note: All weeks are ±3 days compared to Baseline. Week 0 of the alternative schedule starts 2 weeks after the last dose of the double-blind study treatment.
Note: Local guidelines on initiation and monitoring of the particular treatment should be followed.

[a] FU: 8 weeks after Week 52/WD visit.
[b] Subjects will be encouraged to be in fasting condition at the time the subject shifts to alternative treatment, for Apo A1, ApoB, and lipoprotein(a) assessments.
[c] HbA1c will be measured at wdt Week 0.
[d] If the last Q12W assessment for a subject who discontinues study treatment is ≤4 weeks before the final assessments visit at Week 52/WD, the assessment should be cancelled and the subject should instead be invited to undergo the final assessments visit at Week 52/WD (the Week 52/WD visit is to be scheduled 52 weeks [±3 days] after Baseline).
[e] For registration of visit only. Interactive Response System won't assign any open treatment medication.
[f] Follow the regimen of the particular alternative treatment. Arrange for additional site visits for administration and record the treatment in the Concomitant Medication eCRF as appropriate.
[g] Pregnancy testing must be carried out for women of childbearing potential and will be a serum test at the FU visit and a urine test (dipstick) at wdt Week 0 and Week 52/WD visit.

At any time during the study course, but preferably not before Week 12, the Investigator may discontinue the double-blind study treatment and start open-label treatment with either CZP (which will be provided free of charge by UCB) or an alternative drug (eg, other treatment [including biologics]).

The determination by the Investigator to switch a subject from double-blind study treatment to either open-label CZP or other treatment will generally be done after the subject has completed the assessments at a given scheduled study visit. That study visit then becomes the withdrawal treatment (wdt) Week 0 visit of the given alternative schedule of assessments. Since many of the assessments required at the wdt Week 0 visit may have already been completed as part of the originally scheduled study visit, only those not already done at that visit should be completed. Table 5–4 outlines which additional study assessments would be required at wdt Week 0 for subjects switching to the open-label CZP alternative schedule, and Table 5–5 shows this information for subjects switching to the other treatment alternative schedule.

It may be possible that an Investigator determines that a subject should switch to the alternative schedule with either open-label CZP or another treatment without initiating the alternative treatment at the study visit when this determination is made. In this case, the subject will come back another day shortly thereafter to initiate the treatment and to complete all assessments outlined on the relevant alternative schedule of assessments (see Table 5–4 or Table 5–5) for the wdt Week 0 visit. It is important then to schedule the wdt Week 0 and the subsequent on-site visits accordingly in order to end up at Week 52 with the same visit date as originally planned for the regular double-blind study course.

Table 5–4: Schedule of study assessments – additional assessments for wdt 0 visit required for subjects transitioning to open-label CZP

Visit #[a]	1/ BL	2	3	4	5	6	7	8	9 H	10	11 H	12	13 H	14	15 H	16	17 H	18	19 H	20	21 H	22	23 H	24	25 H	26	27
Week **Protocol Activity**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14 /H**	**16**	**18 /H**	**20**	**22 /H**	**24**	**26 /H**	**28**	**30 /H**	**32**	**34 /H**	**36**	**38 /H**	**40**	**42 /H**	**44**	**46 /H**	**48**	**50**
Vital signs									X		X		X		X		X		X		X		X		X		
Hematology/urine/ biochemistry					X		X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
CRP					X		X		X		X		X		X		X		X		X		X		X		X
Pregnancy testing					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PE					X		X		X		X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
TB questionnaire					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
BASMI & spinal mobility					X		X		X		X		X		X		X		X		X		X		X		X
BASDAI					X		X		X		X		X		X		X		X		X		X		X		X
BASFI					X		X		X		X		X		X		X		X		X		X		X		X
SF-36					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		X
ASQoL					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		X
MOS Sleep Scale					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		X
EQ-5D					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		X
MASES					X		X		X		X	X	X		X	X	X		X	X	X		X	X	X		X
Total and nocturnal spinal pain					X		X		X		X		X		X		X		X		X		X		X		X
Swollen and tender joint counts					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
PhGADA					X		X		X		X		X		X		X		X		X		X		X		X
PGADA					X		X		X		X		X		X		X		X		X		X		X		X

Table 5–4: Schedule of study assessments – additional assessments for wdt 0 visit required for subjects transitioning to open-label CZP

Visit #[a]	1/ BL	2	3	4	5	6	7	8	9 H	10	11 H	12	13 H	14	15 H	16	17 H	18	19 H	20	21 H	22	23 H	24	25 H	26	27
Week **Protocol Activity**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14 /H**	**16**	**18 /H**	**20**	**22 /H**	**24**	**26 /H**	**28**	**30 /H**	**32**	**34 /H**	**36**	**38 /H**	**40**	**42 /H**	**44**	**46 /H**	**48**	**50**
CZP plasma concentration/anti-CZP Abs/Biomarker					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
IXRS									X		X		X		X		X		X		X		X		X		
Study drug administration sc																											

Abs=antibodies; ASQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; BL=Baseline; CRP=C reactive protein; CZP=certolizumab pegol; EQ‑5D=EuroQoL Health Status Questionnaire (5 dimensions); H=home; IXRS=Interactive Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MOS=Medical Outcomes Study; PE=physical exam; PhGADA=Physician's Global Assessment of Disease Activity; PGADA=Patient's Global Assessment of Disease Activity; sc=subcutaneously; SF‑36=Short‑Form 36‑item Health Survey; TB=tuberculosis; wdt=withdrawal treatment

[a] Additional assessments to be performed correspond to the assessments to be performed at wdt Week 0.

Table 5–5: Schedule of study assessments – additional assessments for wdt 0 visit required for subjects transitioning to alternative treatment

Visit #[a]	1/ BL	2	3	4	5	6	7	8	9 H	10	11 H	12	13 H	14	15 H	16	17 H	18	19 H	20	21 H	22	23 H	24	25 H	26	27
Week **Protocol Activity**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14 /H**	**16**	**18 /H**	**20**	**22 /H**	**24**	**26 /H**	**28**	**30 /H**	**32**	**34 /H**	**36**	**38 /H**	**40**	**42 /H**	**44**	**46 /H**	**48**	**50**
Hematology/urine/ biochemistry					X		X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
CRP					X		X		X		X		X		X		X		X		X		X		X		X
PE					X		X		X		X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
BASDAI					X		X		X		X		X		X		X		X		X		X		X		X
BASFI					X		X		X		X		X		X		X		X		X		X		X		X
Total and nocturnal spinal pain					X		X		X		X		X		X		X		X		X		X		X		X
PhGADA					X		X		X		X		X		X		X		X		X		X		X		X
PGADA					X		X		X		X		X		X		X		X		X		X		X		X
CZP plasma concentration/ anti-CZP Abs/ Biomarker					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
IXRS									X		X		X		X		X		X		X		X		X		

Abs=antibodies; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BL=Baseline; CRP=C reactive protein; CZP=certolizumab pegol; H=home; IXRS=Interactive Response System; MOS=Medical Outcomes Study; PE=physical exam; PhGADA=Physician's Global Assessment of Disease Activity; PGADA=Patient's Global Assessment of Disease Activity; sc=subcutaneously; wdt=withdrawal treatment

[a] Additional assessments to be performed correspond to the assessments to be performed at wdt Week 0.

Table 5–6: Schedule of study assessments - Safety Follow-Up Extension Period

Visit #	29	30	31	32	33	34	35	36	37	38	39	40
Overall Study Week/SFE Week Protocol Activity	**52/0**[a]	**54/2**	**56/4**	**64/12**	**76/24**	**88/36**	**100/48**	**112/60**	**124/72**	**136/84**	**148/96**	**156/104/WD**
Informed consent[b]	X											
AEs		X	X	X	X	X	X	X	X	X	X	X
IXRS[c]	X	**X**	**X**	X	X	X	X	X	X	X	X	X
Study drug loading dose administration sc[d]	X	X	X									
Study drug dispensation[e]	X			X	X	X	X	X	X	X	X	

AEs=adverse events; CZP=certolizumab pegol; FU=Follow-Up; IXRS=Interactive Response System; SFE=Safety Follow-Up Extension; WD=Withdrawal;

[a] Assessments performed at the Week 52 Visit for subjects who completed the previous Double-Blind Period are in Table 5–1; Assessments performed at the Week 52 Visit for subjects who transitioned to open-label CZP treatment after withdrawal from the Double-Blind Period are in Table 5–2.

[b] A separate informed consent form will be obtained from subjects consenting to participate in the SFE Period.

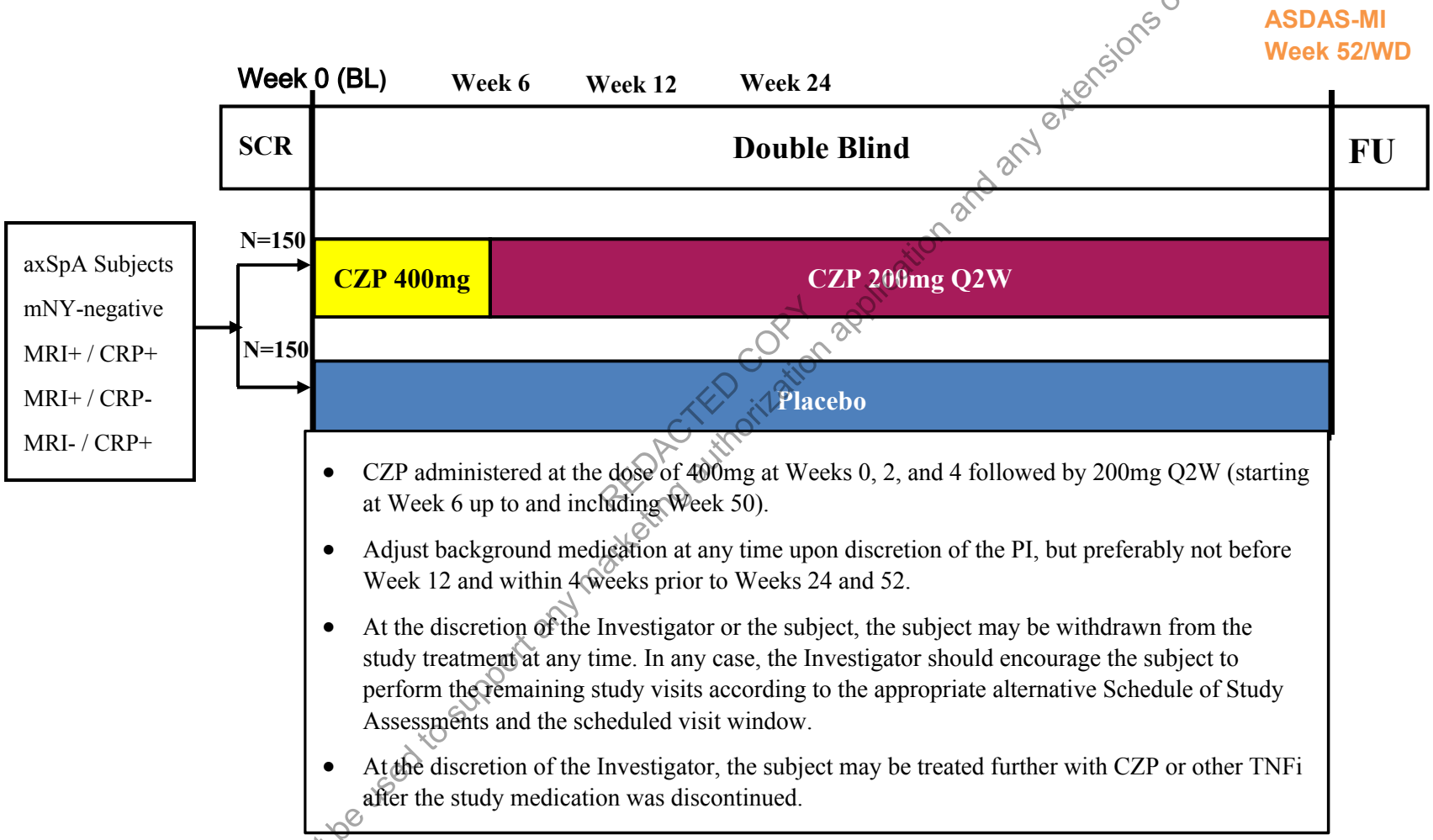
[c] Contact IXRS to register the visit and obtain next kit number, where applicable, or to indicate that the subject has completed the SFE Period or withdrawn from the study.

[d] At Weeks 52, 54, and 56, study treatment administration should be performed at the site by unblinded study personnel in order to keep the blind (see Section 7.2.1).

[e] Starting at Week 52 for subjects completing open-label CZP treatment and the Week 52 visit, dispense the assigned study medication to the subject for use at home, as appropriate.

5.3 Schematic diagram

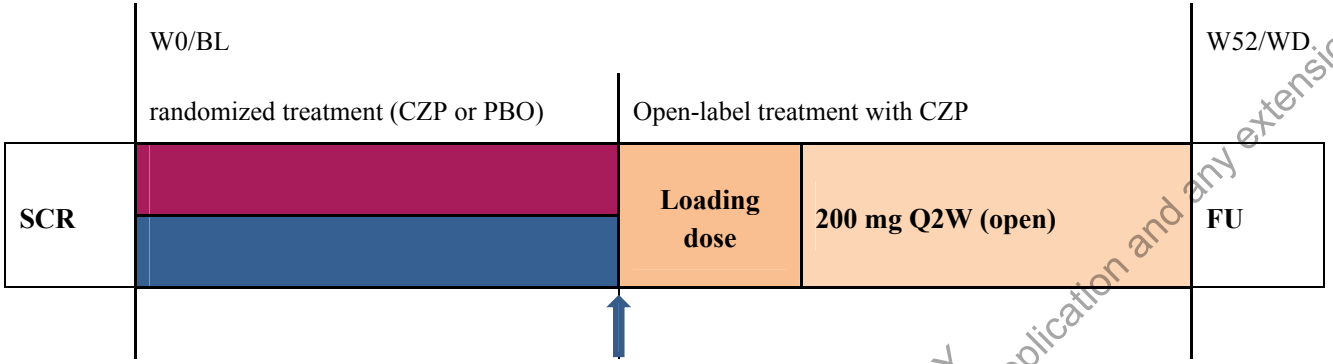
Figure 5–1: Schematic diagram for subjects completing the double-blind study treatment



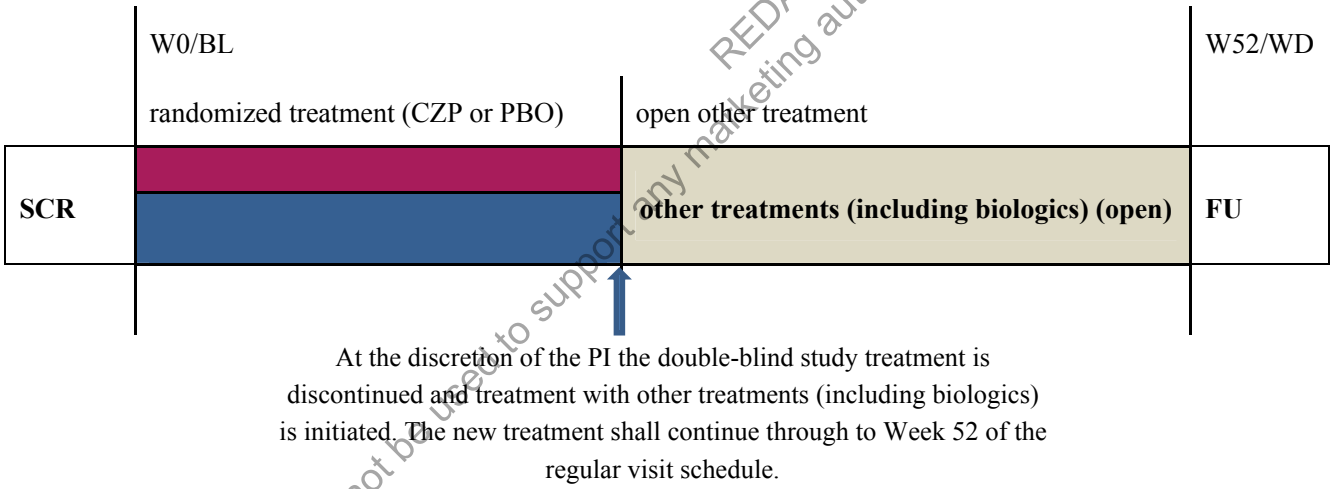
ASDAS-MI=Ankylosing Spondylitis Disease Activity Score major improvement; axSpA=axial spondyloarthritis; BL=Baseline; CRP=C-reactive protein; CZP=certolizumab pegol; FU=Follow-Up; mNY=modified New York criteria; MRI= magnetic resonance imaging; N=number of subjects; PI=Principal Investigator; Q2W=every 2 weeks (every other week); SCR=Screening; TNFi=tumor necrosis factor-alpha inhibitor; WD=withdrawal

Figure 5–2: Schematic diagram for subjects discontinued from the double-blind study treatment

Scenario A: The subject initiates treatment with CZP for treatment to be supplied to discontinued subjects

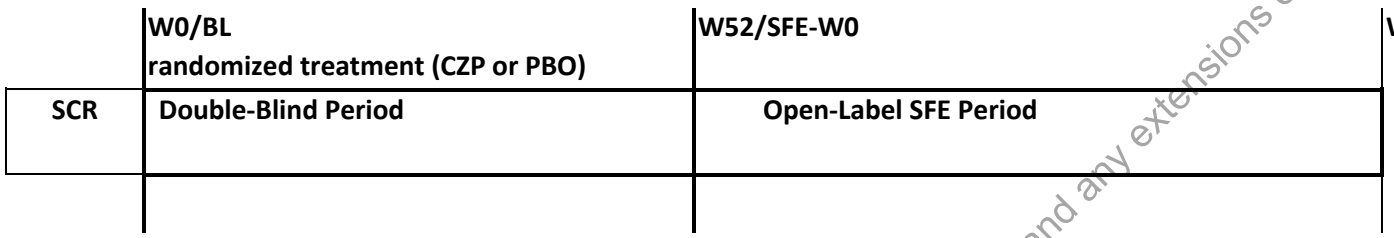


Scenario B: The subject initiates treatment with other treatments (including biologics)



BL=Baseline; CZP=certolizumab pegol; FU=Follow-Up; PBO=placebo; PI=Principal Investigator; Q2W=every 2 weeks (every other week); SCR=Screening; W=week; WD=withdrawal

Figure 5–3: Schematic diagram for subjects completing the double-blind study treatment and rolling over to the SFE Period



BL=Baseline; CZP=certolizumab pegol; FU=Follow-Up; SFE=Safety Extension; PBO=placebo; SCR=Screening; SFE=safety Follow-Up Extension; W=week

Note: Subjects who complete either double-blind treatment or open-label CZP-treatment and all assessments at Week 52 are eligible to roll-over to the SFE Period. Subjects who complete alternative treatment must finish the study at Week 52 and be scheduled for the final FU visit (8 weeks after the Week 52 visit).

5.4 Rationale for study design and selection of dose

The current study will evaluate nr-axSpA subjects receiving either CZP or placebo in combination with standard of care for a duration of 52 weeks. This is a unique study design to achieve an understanding of the natural history of nr-axSpA and to support the assumption that treatment with a TNFi is necessary in this group of subjects. The lack of a mandatory escape arm for placebo subjects is balanced by the ability of the Investigators to modify background medications (NSAIDs, corticosteroids, analgesics, and SAARDs) during the course of the study. If the Investigator determines that a subject should be treated with other medicines (including biologics), the study medication will be discontinued and subjects will be asked to continue to come to the office for study visits to track their response to other treatments. If the Investigator choses to withdraw subjects on the other therapy, the local guidelines on initiation and monitoring of the particular treatment should be followed.

In accordance with prescribing information for CZP, 3 loading doses of 400mg Q2W should be administered upon initiation of therapy. Thus all subjects who withdraw from double-blind treatment prior to Week 52 and transition to open-label CZP within the AS0006 study will receive this loading dose prior to the maintenance dose of 200mg Q2W. It is recognized that some subjects would have been on active CZP prior to transition to open-label CZP. However, this dosing approach is justified in all transitioning subjects as there will be no change in benefit-risk due to administration of loading dose and the blinding will be maintained in the study, preserving the data integrity.

The enrollment criteria will result in the following subgroups based on MRI and CRP:

- MRI+/CRP+
- MRI+/CRP-
- MRI-/CRP+

This 3-level MRI/CRP classification variable will be used as a stratification factor in the randomization to ensure balance across these subgroups. Taken together, these 3 subgroups encompass the nr-axSpA subject population that would benefit most from anti-TNF therapy and who have the most limited treatment options.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject or legal representative. The
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete questionnaires), visit schedule, or medication intake according to the judgment of the Investigator.
3. Subject is at least 18 years old at the Screening visit.

4. Female subjects must be either postmenopausal for at least 1 year, surgically incapable of childbearing, or effectively practicing an acceptable method of contraception (either oral/parenteral/implantable hormonal contraceptives, intrauterine device, or barrier and spermicide). Abstinence only is not an acceptable method. Subjects must agree to use adequate contraception during the study and for at least 10 weeks (or [for participating countries of the EU – 5 months in accordance with the Summary of Product Characteristics, SPC] longer if required by local regulations) after the last dose of study treatment. Male subjects must agree to ensure they or their female partner(s) use adequate contraception during the study and for at least 10 weeks (or [for participating countries of the EU - 5 months in accordance with the SPC] longer if required by local regulations) after their last dose of study treatment.
5. Subjects must have a documented diagnosis of adult-onset axSpA and meet the ASAS criteria for axSpA (not including family history and good response to NSAIDs; see Appendix 18.1).
6. Subjects must have had back pain for at least 12 months before Screening.
7. Subjects must NOT have sacroiliitis defined by mNY criteria (see Appendix18.2) (bilateral ≥Grade 2; unilateral ≥Grade 3) on SI joint x-rays (based on central reading of x-rays, within the last 12 months from Baseline).
8. Subjects must have active disease as defined by each of the following at Screening and Baseline:
   - BASDAI score ≥4
   - Spinal pain ≥4 on a 0 to 10 NRS (from BASDAI item 2)
9. Subjects must have a combination of current evidence of sacroiliitis on the screening MRI as defined by ASAS/OMERACT scoring confirmed via central reading (MRI+) and CRP either >upper limit of normal (ULN) or ≤ULN (for CRP the ULN is defined as the ULN indicative for inflammatory disease) at Baseline (CRP+ or CRP-), or no evidence of sacroiliitis on the screening MRI (MRI-) and CRP >ULN (CRP+) as follows:
   - MRI+/CRP+
   - MRI+/CRP-
   - MRI-/CRP+
10. Subjects must have had an inadequate response to, have a contraindication to, or have been intolerant to at least 2 NSAIDs. Inadequate response to an NSAID is defined as lack of response to at least 14 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID.

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

1. Subject has previously participated in this study or subject has previously been assigned to treatment in a study of the medication under investigation in this study.

2. Subject has participated in another study of an investigational medicinal product (IMP) (or a medical device) within the previous 3 months (or 5 half-lives, whichever is greater) or is currently participating in another study of an IMP (or a medical device).
3. Subject has history of chronic alcohol abuse or drug abuse within the last year.
4. Subject has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the subject's ability to participate in this study.
5. Subject has a known hypersensitivity to any components of the IMP or comparative drugs as stated in this protocol.

Axial SpA-disease-related exclusions

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

Prior medications exclusions

9. Subjects must not have used the following medications in the manner as detailed by the exclusion criteria in the following table (see Table 7–1).

Previous clinical studies and previous biological therapy exclusions

10. Subjects must not have received any nonbiological therapy for axSpA not listed in Table 7–1 within or outside a clinical study in the 3 months or within 5 half-lives prior to the Baseline visit (whichever is longer).
11. Subjects must not have received any experimental biological agents (defined as those agents unlicensed for use in axSpA in Europe or the USA).
12. Subjects must not have received previous treatment with a PEGylated compound that resulted in a severe hypersensitivity reaction or an anaphylactic reaction.
13. Subjects may not have been exposed to more than 1 TNFi prior to the Baseline visit and may not be a primary failure to any TNFi therapy (defined as no response within the first 12 weeks of treatment with the TNFi).

Medical History Exclusions

14. Female subjects who are breastfeeding, pregnant or plan to become pregnant during the study or within 3 months following the final dose of the investigational product.
15. Subjects with a history of chronic or recurrent infections (more than 3 episodes requiring antibiotics or antivirals during the preceding year), recent serious or life–threatening infection within the 6 months prior to the Baseline visit (including hospitalization for any infection in the last 6 months or any current sign or symptom that may indicate an infection).
16. Subjects with a history of herpes zoster infection within 6 months prior to the Baseline visit.

17. Subjects with known TB infection, at high risk of acquiring TB infection, or LTB infection are excluded.

a. Known TB infection whether present or past is defined as:

   i) Active TB infection or clinical signs and symptoms suspicious for TB (pulmonary or extra-pulmonary)

   ii) History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection

   iii) Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the subject's medical history.

b. High risk of acquiring TB infection is defined as:

   i) Known exposure to another person with active TB infection within the 3 months prior to Screening

   ii) Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high.

c. Latent TB infection (unless appropriate prophylaxis is initiated prior to study treatment and continued to completion of prophylaxis). Please refer to Section 12.6.3 for further details and instructions.

18. Subjects with concurrent acute or chronic viral hepatitis B or C or with human immunodeficiency virus (HIV) infection.

19. Subjects with history of or current active infection with Histoplasma, Coccidiodes, Paracoccidioides, Pneumocystis, nontuberculous mycobacteria (NTMB), Blastomyces, or Aspergillus.

20. Subjects must not have a history of an infected joint prosthesis at any time.

21. Subjects receiving any live (includes attenuated) vaccination within the 8 weeks prior to Baseline (eg, inactivated influenza and pneumococcal vaccines are allowed but nasal influenza vaccination is not permitted).

22. Subjects who in the Investigator's opinion have a high risk of infection (eg, subjects with leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections, and subjects who are permanently bedridden or wheelchair bound).

23. Subjects with a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.

24. Concurrent malignancy or a history of malignancy (subjects with less than 3 excised basal cell carcinomas or with cervical carcinoma in situ successfully surgically treated more than 5 years prior to Screening may be included).

25. Subjects with Class III or IV congestive heart failure as per the New York Heart Association (NYHA) 1964 criteria.

26. Subjects with a history of, or suspected, demyelinating disease of the central nervous system (eg, multiple sclerosis or optic neuritis).

27. Subjects having had major surgery (including joint surgery) within 8 weeks prior to Screening, or having planned surgery within 6 months after entering the study.
28. Subjects with a current or recent history, as determined by the Investigator, of severe, progressive, and/or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, or neurological disease.
29. Subjects with significant laboratory abnormalities, including but not limited to:
    - liver function tests >2.0xULN
    - estimated Glomerular Filtration Rate as measured by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI; Levey et al, 2009) <60mL/min/1.73m^2
    - white blood cell ([WBC] <3.0x10^9/L).
30. Subjects with any other condition which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study.

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care.

Subjects should be withdrawn from the study if any of the following events occur:

1. Subject develops an illness that would interfere with his/her continued participation.
2. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. Subject withdraws his/her consent.
4. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test (see Section 12.1.6 for more information regarding pregnancies).
5. The Sponsor or a regulatory agency requests withdrawal of the subject.
6. Subject's subsequent TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). Refer to Section 12.6.3 for further details and instructions.

Subjects should be withdrawn from the study-treatment if,

7. The Investigator decides to initiate an alternative treatment due to an unsatisfactory response to the study treatment, or
8. Subjects take any of the prohibited medications in Table 7–1 and Section 7.8.2

If a subject is withdrawn from the double-blind study treatment, the Investigator should encourage the subject to continue participation in the study in accordance with the appropriate alternative schedule of study assessments (Table 5–2 or Table 5–3). The treatment that the subject receives following withdrawal of study medication is at the discretion of the Investigator, with open-label CZP available as a treatment option according to the local requirement mandated in the region. UCB will provide this medication free of charge. Alternatively, the Investigator may treat the subject with other treatments (including biologics) as deemed appropriate by local

regulations. If the Investigator chooses to withdraw subjects on the other therapy, the local guidelines on initiation and monitoring of the particular treatment should be followed.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject from the double-blind study treatment in advance. The reason for discontinuation of the double-blind study treatment must be recorded in the CRF as appropriate.

Although the subject may be withdrawn from the double-blind study treatment at any time, every effort should be made to retain the subject in the study and encourage compliance of the subject with the scheduled study visits. For subjects who fail to return to study visit(s) or are considered lost to follow up, the Investigator should specifically communicate (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents). In case the attempts to direct contact the subject fail, the Investigator is encouraged to gain information about the wellbeing of the subject at the end of the regular visit schedule (Week 52/WD) from other sources in compliance with local regulations. All results of observations and communication with the subject, including and not limited to the relevant information on his/her wellbeing, must be recorded in the source documents.

If a subject is withdrawn from the study, the narrative description of the reason(s) for removing the subject must be recorded in the source documents. The CRF must document the primary reason for withdrawal.

Subjects withdrawn from the study will not be replaced.

6.4 Eligibility for the SFE Period

To be eligible to participate in the SFE Period, subjects on double-blind study treatment and subjects who withdrew from double-blind study treatment and transitioned to open-label CZP treatment must complete all of the Week 52 visit assessments. Subjects on alternative treatments are not eligible to participate in the SFE Period.

Eligible subjects are allowed to roll-over to the SFE-Period up to 3 months after completion of the Week 52 assessments.

Prior to initiating the SFE assessments, all subjects will be asked to read and sign a separate informed consent form.

Questions concerning the eligibility of a subject to continue participation in the study should be made in consultation with the Medical Monitor.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal product(s)

The IMP (double-blind study treatment: CZP or placebo), will be supplied under the responsibility of the UCB Clinical Supply Unit. The frequency at which IMP will be supplied to each individual center will be adapted to the recruitment capacity of that center and to the expiry date of the IMP and will be managed by the interactive response system (IXRS).

Drug supplies will consist of the following:

Certolizumab pegol is supplied as a sterile, clear, colorless to slightly yellow liquid solution with a pH of approximately 4.7 in 1mL single use glass prefilled syringe (PFS) with a 25G ½ inch thin wall needle for sc injection. Each syringe contains an extractable volume of 1mL at a concentration of 200mg/mL of CZP in 10mM sodium acetate buffer and 125mM sodium chloride as a tonicity agent.

Placebo is supplied in a PFS with a 25G ½ inch thin wall needle, containing an injectable volume of 1mL 0.9% saline for single use.

Due to the difference in presentation and viscosity between CZP and placebo, special precautions will be taken in order to ensure maintained blinding of the study (unblinded/blinded site personnel and monitors).

7.2 Treatment(s) to be administered

Treatments to be administered are as described in Section 5.1.

7.2.1 Treatment administration

A pharmacy manual will be provided to each site containing instructions regarding drug preparation and dosing. The injection schedule through Week 52 is presented in Figure 7–1. The injection schedule for the SFE Period is presented in Figure 7–2.

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site. At the Week 0, 2, 4, 6, and 8 visits, the administration must be done by dedicated, unblinded, and adequately trained site personnel. At the Week 10 and 12 visits, the subject will receive training on self-injection and the study treatment will be self-administered under the supervision of the unblinded study personnel. At Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50, the study treatment administration should preferably be done by the unblinded study personnel, or alternatively by self-injection of the subject under the supervision of the unblinded study personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46.

Injections should be administered with a minimum of 10 days between the CZP 200mg Q2W injections.

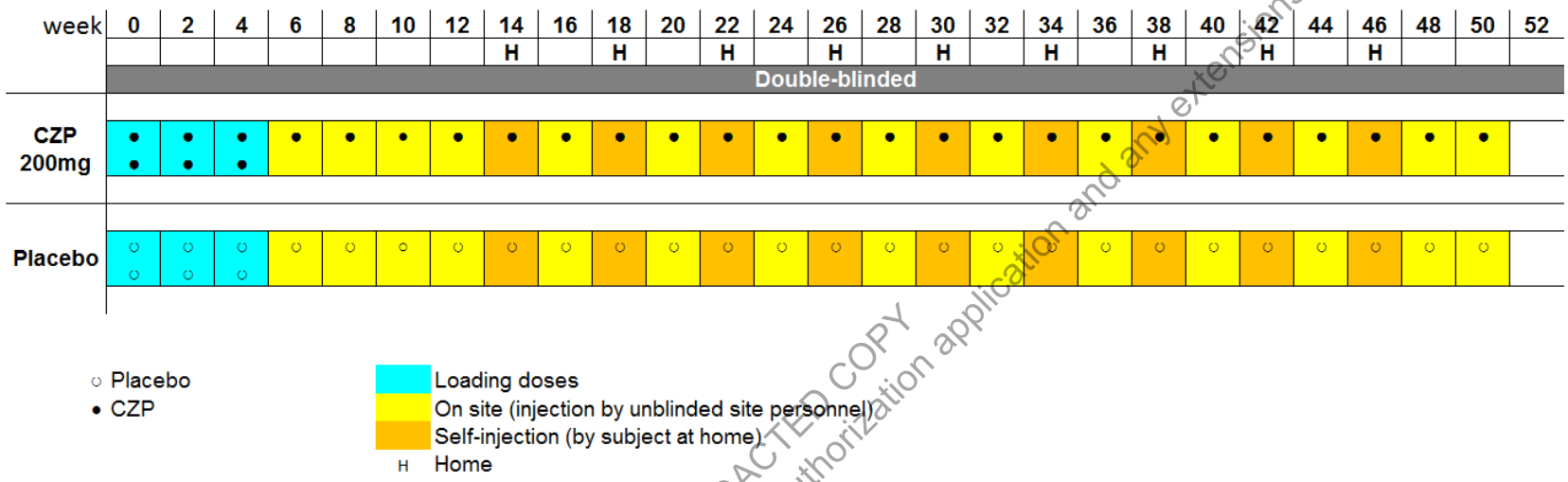
During the SFE Period, CZP will be administered sc by dedicated unblinded study personnel at the study site on Weeks 52, 54, and 56 for subjects completing double-blind treatment in order to maintain the blind. Subjects who complete the Week 52 visit on placebo treatment will receive loading doses of CZP 400mg at these visits. Subjects who complete the Week 52 visit on CZP treatment will receive 1 injection of CZP 200mg and 1 injection of placebo at these visits to continue their previous CZP treatment regimen.

Subjects who withdrew from double-blind study treatment and transitioned to open-label CZP treatment do not need to visit the site at Week 54 and Week 56, and should continue their open-label CZP treatment regimen.

For the remainder of the SFE Period, CZP can be administered at the site by dedicated study personnel, or by self-injection of the subject under the supervision of the dedicated study personnel, or subjects may self-administer their study treatment Q2W at home.

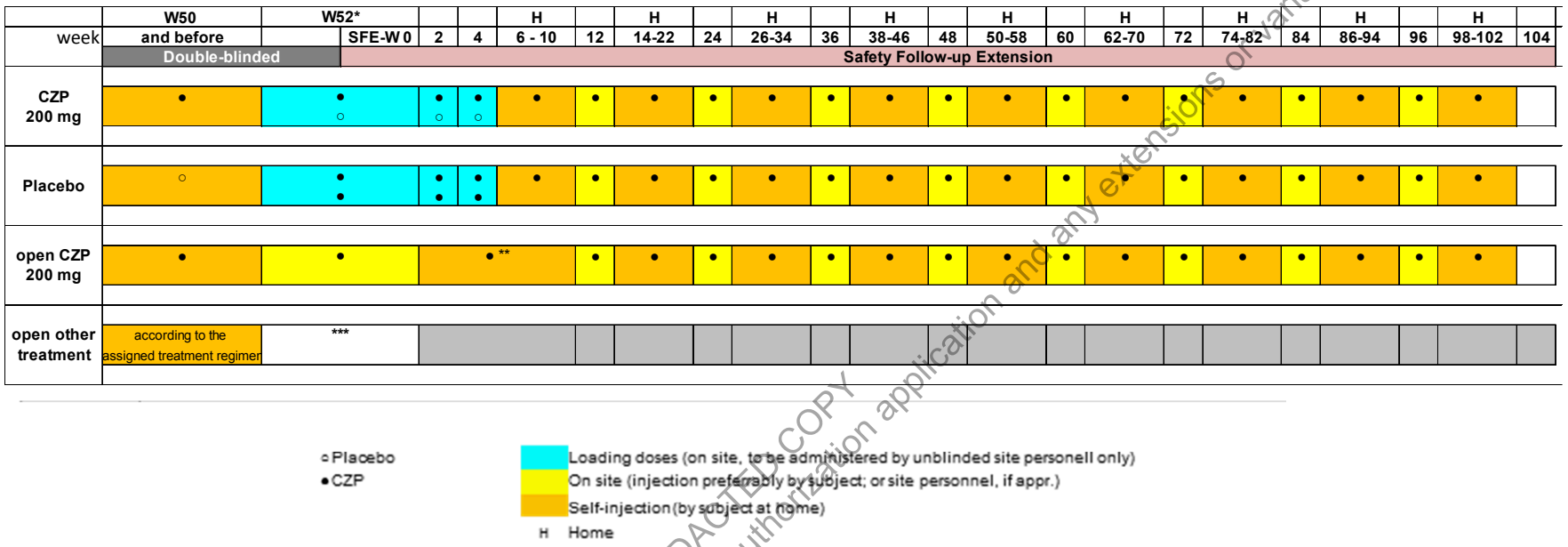
7.2.2 Study AS0006 injection schedule

Figure 7–1: Injection schedule through Week 52



CZP=Certolizumab pegol; H=home

Figure 7–2: Injection schedule for the SFE Period



CZP=Certolizumab pegol; FU=follow-up; H=home; SFE=Safety Follow-Up Extension; W=week

* Subjects who complete either double-blind treatment or open-label CZP-treatment and all assessments at Week 52 are eligible to roll-over to the SFE Period. Subjects who complete alternative treatment must finish the study at Week 52 and be scheduled for the final FU visit (8 weeks after the Week 52 visit).

** Subjects rolling over from open-label CZP-treatment to the SFE Period can self-administer their study medication at home from Weeks 2 to 10.

*** Subjects will complete the study assessments at Week 52 according to the protocol and be invited for the final FU visit 8 weeks after Week 52.

7.3 Packaging

Certolizumab pegol and placebo are packaged and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. They are suitably packaged in such a way as to protect the IMP from deterioration during transport and storage.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language. Details on Labeling will be provided in the Pharmacy manual.

7.5 Handling and storage requirements

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. The IMP stored by the Investigator is to be kept in a secured area with limited access. The IMP containers should be stored at 2 to 8°C and protected from light. Additional information regarding the receipt of the drug and return handling will be specified in the Pharmacy Manual.

Appropriate storage conditions must be ensured by a controlled temperature and by completing a temperature log in accordance with local requirements but at least once per working day with minimum and maximum temperatures reached over the time interval.

In case an out of range temperature is noted, it must be immediately communicated to the Sponsor' designee in accordance with the Pharmacy Manual.

The Investigator (or designee) will instruct the subject to store the IMP following the instructions on the label.

Detailed information on handling and storage of IMP will be given in the Pharmacy Manual.

7.6 Drug accountability

A drug accountability form will be used to record IMP dispensing and return information during the course of the study. Details of any drug lost (due to breakage or wastage), not used, disposed of at the study site, or returned must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) and unused IMP containers must be reconciled and returned to UCB (or designee), preferably in their original packaging. Instructions on how to use and store the IMP will be provided. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the IMP is used only in accordance with the protocol.

All study drug documentation (eg, shipping receipts, drug accountability logs, IXRS randomization materials) must be maintained and accessed by unblinded, trained site personnel only. Designated, unblinded site personnel must be appropriately trained and licensed (per country guidelines) to administer injections. Each site will be required to have a written blinding plan in place signed by the Principal Investigator, which will detail the site's steps for ensuring that the double-blind nature of the study is maintained from Week 0 to Week 52/WD.

7.7 Procedures for monitoring subject compliance

Drug accountability must be recorded on the drug accountability form.

If a subject is found to be persistently noncompliant (missing 3 or more doses over any period of 52 weeks), the subject will be withdrawn from the study. A subject will be withdrawn from the study if 3 consecutive doses were missed prior to the primary endpoint assessment. No missing doses are allowed in the first 12 weeks of the study. Doses of IMP that were missed due to a reasonable interfering AE that does not allow administration of an anti-TNF due to safety reasons will not be considered for the evaluation of subject compliance. Evaluation of the reasonability of the AE must be discussed immediately with the Medical Monitor.

7.8 Concomitant medication(s)/treatment(s)

For any subject taking any medication, including over the counter products, nutraceuticals, or herbal medications at Screening or at any time during the course of the study, an accurate record must be kept in the clinic chart (source documentation) and the CRF. This record should include the name of the drug, the dose, the date(s) of administration, and the indication for use.

Changes in the concomitant medication to treat the burden of the predominantly existing disease of the nr-axSpA symptoms is allowed during the Placebo-Controlled Period of the study under the conditions listed below. A change in the first 12 weeks of the study should be avoided.

Table 7–1: Concomitant Medications (prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
Analgesics (including, but not limited to acetaminophen, paracetamol, opiates, or combinations thereof)	Up to maximum approved dose	Any change in stable dose regimen is excluded in the 14 days prior to the Baseline visit.	Any ad hoc (prn) use of analgesics is not permitted within 24 hours prior to any post-Screening visit. An increase or addition in opiates or a combination with opiates is not recommended between Week 0 and Week 12 or within 4 weeks prior to the Week 24 or Week 52 visits.

Table 7–1: Concomitant Medications (prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
NSAIDs (including COX-2 inhibitors)	Up to maximum approved dose regimen	Any change in stable dose regimen is excluded in the 14 days prior to the Baseline visit.	Any ad hoc (prn) use of NSAIDs is not permitted within 24 hours prior to any post-Screening visit. Changes in NSAID doses should be avoided between Week 0 and Week 12 or within 4 weeks prior to the Week 24 or Week 52 visits.
Oral corticosteroids	Maximum allowed ≤10mg daily total prednisone equivalent[a]	Any change in stable dose used for axSpA in the 28 days prior to the Baseline visit. If a taper of oral corticosteroids is planned this should be completed 14 days prior to Baseline visit.	Maximum allowed ≤10mg daily total prednisone equivalent[a] Changes in dose or initiation of corticosteroids (including tapers) should be avoided between Week 0 and Week 12 or within 4 weeks prior to the Week 24 or Week 52 visits.
Corticosteroids (im)	Any dose	Use in the 28 days prior to the Baseline visit.	Corticosteroids (im) must not be used during the study.
Corticosteroids (ia)	Up to maximum approved dose	Use in the 28 days prior to the Baseline visit.	SIJ corticosteroid (ia) injections are not allowed during the study. Peripheral joint injections are permitted.

Table 7–1: Concomitant Medications (prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
Corticosteroids (iv)	Up to maximum approved dose	Use in the 28 days prior to the Baseline visit.	Doses of corticosteroids (iv) may be used during the study for acute illnesses as long as the dose is not given within 1 week prior to Week 12, Week 24, or Week 52 and the underlying disease does not present a contraindication to the subject remaining in the study. Indications might include dermatitis, gastroenteritis, asthma exacerbation, and pneumonia.
Hyaluronic acid (ia)	Any dose	Use in the 28 days prior to the Baseline visit.	Used in knee as needed after Week 12 visit.
SAARDs[b]: SSZ and/or HCQ and/or MTX and/or LFN and/or AZA	Maximum allowed: SSZ ≤3g daily HCQ ≤400mg daily MTX ≤25mg weekly AZA ≤150mg/day LFN ≤20mg/day	SAARD initiated and or any change in the dose regimen in the 28 days prior to the Baseline visit.	Changes in SAARD doses should not be made between Week 0 and Week 12 or within 4 weeks prior to Week 24 or Week 52 visit. SAARD dose reduction to manage intolerance or safety issues is allowed at any time during the study at the Investigator's discretion.
SAARDs: cyclosporine, cyclophosphamide, mycophenolic acid, apremilast	Up to maximum approved dose	Use within 28 days prior to the Baseline visit	Changes in SAARD doses or initiation of a new SAARD should be avoided between Week 0 and Week 12 or within 4 weeks prior to Week 24 or Week 52 visit

Table 7–1: Concomitant Medications (prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
Anti-TNF therapies IFX ADA ETN GOL CZP	Any dose	Only 1 previous biologic is allowed. For IFX, ADA, and GOL, any use within the 3 months prior to the Baseline visit. For ETN, use within the 28 days prior to the Baseline visit. For CZP any exposure history.	If biologic therapy is required the subject must be discontinued from study medication and should conduct the remaining visits according to Figure 5–2.
Other rheumatologic therapies: ABA rituximab anti-IL17 tocilizumab ustekinumab tofacitinib biosimilars to any approved biologic	Any dose	Any exposure history.	If other rheumatologic therapies are required the subject should be discontinued from study medication and should conduct the remaining visits according to Figure 5–2.
Osteoporosis medications: eg, risedronate alendronate ibandronate denosumab cathepsin K inhibitor cinacalcet calcitonin	Up to maximum approved dose	All stable osteoporosis medications are permitted except for bisphosphonates (iv).	If the treatment is initiated during the study, the subject should be discontinued from study medication and should conduct the remaining visits according to Figure 5–2. Osteoporosis medications with the exception of bisphosphonates (iv) are allowed without restriction. Bisphosphonates (iv) are not permitted any time within the study.

Table 7–1: Concomitant Medications (prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
Intravenous bisphophonates: zoledronic acid ibandronate pamidronate	Any dose	Zoledronic acid: any use within the 3 years prior to randomization Ibandronate or pamidronate: any use within the past 2 years.	If iv bisphosphonate treatment is initiated during the study, the subject should be discontinued from study medication and should conduct the remaining visits according to Figure 5–2.

ABA=abatacept; ADA=adalimumab; axSpA=axial spondyloarthritis; AZA=azathioprine; COX-2=cyclooxygenase 2; CZP=certolizumab pegol; DMARD=disease-modifying antirheumatic drug; ETN=etanercept; GOL=golimumab; HCQ=hydroxychloroquine; IFX=infliximab; ia=intra-articular; IL=interleukin; im=intramuscular; iv=intravenous; LFN=leflunomide; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; RA=rheumatoid arthritis; SAARD=slow-acting antirheumatic drug; SIJ=sacroiliac joint injection; SSZ=sulfasalazine; TNF=tumor necrosis factor

[a] A table of corticosteroid equivalent doses can be found in Appendix 18.3.

[b] Throughout the text, we refer to compounds such as SSZ and MTX as SAARDs. These medications are also commonly referred to as DMARDs, but since there is no evidence that they are in fact disease-modifying in axSpA (unlike in RA), we have opted for the more appropriate SAARD terminology.

7.8.1 Permitted concomitant treatments for axSpA (medications and therapies)

The Investigator must make decisions regarding changes in background medications based upon the subject's response to previous therapy, medical history and the physician's judgment as to how to manage the axSpA disease symptoms. If possible, the following treatment recommendations for modifying background medications should be considered:

- NSAIDs including cyclooxygenase-2 (COX-2) inhibitors: ad hoc as needed (prn) should not be used 24 hours of any post-Screening study visit. As subjects should be on stable dose of background medication at study entry, a change in the first 12 weeks of the study should be avoided. Changes in dose and type of NSAID should not be made within 4 weeks prior to Week 24 and 52 visits.
- Modify the SAARD if needed to treat peripheral symptoms.
- Specific SAARDs only (SSZ and/or hydroxychloroquine [HCQ] and/or MTX): maximum SSZ ≤3g daily; HCQ ≤400mg daily; MTX ≤25mg weekly allowed. As subjects should be on stable dose of background medication at study entry, a change in the first 12 weeks of the study should be avoided. Changes in SAARDs doses should not be made within 4 weeks before Week 24 or Week 52 visit.
- Stable doses of analgesics (including, but not limited to acetaminophen, paracetamol, NSAIDs, opiates, or combinations thereof) will be permitted except that ad hoc prn usage is prohibited within 14 days of Baseline and no ad hoc use prior to any post-Screening visit. As subjects should be on stable dose of background medication at study entry, a change in the first 12 weeks of the study should be avoided. An initiation of a new chronic opiate or a

combination with opiates is not recommended between Week 0 and Week 12 or within weeks 4 of the Week 24 or Week 52 visits.

- Add or modify the corticosteroids (see Section 7.8.2 for prohibited corticosteroids):
  - Oral (maximum allowed daily total prednisone equivalent dose of ≤10mg). Oral corticosteroid tapers of 14 days prior to Baseline are allowed as long as the maximum daily dose is ≤10mg. Changes in dose or initiation of corticosteroids (including tapers) should be avoided between Week 0 and Week 12 or within 4 weeks prior to Week 24 or Week 52 visits.
  - Corticosteroids administered intravenously (iv) will be permitted for the purposes of stress dosing for a surgical procedure under general or spinal anesthesia. Further they may be used during the study for acute illnesses as long as the dose is not given within a week of an assessment (Week 12, 24 or 52) and the underlying disease does not present a contraindication to the subject remaining in the trial. Indications might include dermatitis, gastroenteritis, asthma exacerbation, and pneumonia.
- Other treatments (including biologics): If the subject requires the start of other treatments (including biologics) at the discretion of the Investigator, the subject must be withdrawn from the blinded study medication. Every effort should be made to retain the subject in the study and encourage attendance at future study visits.
- The Investigator should refrain from making major changes in background medication between Week 0 and Week 12, as much as possible. Major changes in background medications within 4 weeks of Week 24 or Week 52 should be avoided.

Depending on the subject's response to previous therapy, the Investigator may also reduce the assigned background medication. This change should not be made between Week 0 and Week 12. Major changes in background medications should be avoided within 4 weeks prior to Week 24 or Week 52.

If the Investigator discontinues the double-blind study treatment and initiates therapy with CZP, UCB will supply the subject with the CZP. If the decision is made to start a different treatment (including biologics), UCB will not be supplying the medication.

7.8.2 Prohibited concomitant and rescue treatments (medications and therapies)

Prior medication exclusions and washout periods are listed in Section 6.2. In addition, use of the following concomitant medications is prohibited during the study, except where indicated:

- Corticosteroids (administered iv/intra-articular [ia]) are permitted only as described in Section 7.8.1. Intramuscular and sacroliliac joint injection (SIJ) ia corticosteroids are not permitted.
- Hyaluronic acid is permitted for the use in the knee after Week 12.
- Biologicals (TNFi: IFX, ADA, ETN, GOL, abatacept (ABA), commercially available CZP), anti-CD20, tocilizumab, ustekimumab, also any other biological response modifiers are excluded.
- All iv bisphosphonates are excluded.

If the subject requires any of the medications specified in this section, the subject must be discontinued from the study treatment prior to the initiation of these medications. Before starting these therapies the Investigator should contact the Study Physician.

If the subject is discontinued from study treatment in order to initiate other treatments (including biologics), the subject will be encouraged to return to the site for future study visits to continue to collect data important for study integrity.

If the subject initiates therapy with CZP, UCB will supply the subject with CZP. If the decision is made to start a different therapy, UCB will not supply such medication.

Subjects must not participate in any other clinical study for any indication or receive any unauthorized medication during the study period.

The administration of live vaccines is not recommended for subjects treated with TNFi. Live vaccines should not be administered 8 weeks prior to Baseline. If immunization with a live organism based vaccine is considered during the study, the clinician is urged to carefully weigh the risks versus benefits of immunization. If the subject is going to proceed with live organism based immunization, the subject must be withdrawn from the study prior to administration of the vaccine. Such vaccines must be recorded in the respective section of concomitant module of the CRF.

7.8.3 Concomitant medication(s)/treatments during the SFE Period

At the completion of the Week 52 visit assessments, subjects on double-blind study treatment may receive open-label CZP treatment for an additional 2 years during the SFE Period. During this time, CZP will be provided by the Sponsor. Concomitant medication usage during the SFE Period is at the discretion of the Investigator.

7.9 Blinding

Due to differences in presentation and viscosity between CZP and placebo, special precautions will be taken in order to ensure blinding during the Double-Blind Period of the study. The subject will receive the IMP throughout the study duration for each single administration in a sealed box with PFS containing either CZP 200mg or placebo. Packaging and labeling will be done in a way to ensure that the provided box including the PFS will not provide any information about the assigned treatment (CZP 200mg or placebo). Administration of the IMP will be done according to the schedule of study assessments (Table 5–1) either on-site by appropriately trained unblinded study personnel or at home by the subject him/herself. Pharmacokinetic and antibody data will be provided only after the study is unblinded.

7.9.1 Maintenance of study treatment blind

All subject treatment details will be allocated and maintained by the IXRS.

The study will be double-blind and placebo-controlled for 52 weeks. No study team member involved in the clinical conduct will have access to the randomization schedule until after database lock and unblinding.

If the Investigator decides to discontinue the double-blind study treatment and initiate open-label treatment with CZP or other treatment (including biologics), efforts will be made to ensure that the blinding of the previously assigned double-blind study treatment will be maintained. Therefore, if the open-label treatment with CZP is chosen by the Investigator, the 3 loading doses

of CZP 400mg Q2W will be administered by dedicated study personnel without disclosing to the subject the use of the PFS. After the last loading dose, the subject can self-administer CZP until Week 52/WD of the regular visit schedule.

For the SFE Period, in order to maintain the blind for subjects completing the Double-Blind Period, study treatment will be administered sc by unblinded study staff at the study site on Weeks 52, 54, and 56. Subjects who completed the Week 52 visit on placebo treatment will receive loading doses of CZP 400mg at these visits. Subjects who completed the Week 52 visit on CZP treatment will receive 1 injection of CZP 200mg and 1 injection of placebo at these visits to continue their previous CZP treatment regimen.

7.9.2 Breaking the treatment blind in an emergency situation

All Sponsor, Investigator site, and Contract Research Organization (CRO) staff involved with the study will be blinded to the treatment code until the database lock ie, after completion of the Double-Blind Period with the following exceptions:

- Sponsor clinical study supplies coordinator, packager, and qualified person
- Pharmacy monitors that monitor unblinded pharmacy documentation
- Sponsor pharmacovigilance staff reporting serious adverse events (SAEs) to regulatory authorities
- Laboratory staff analyzing blood samples for CZP plasma concentrations and anti-CZP antibodies
- Site study drug administrator

The appropriate persons (Investigators, Single Safety Case Management [SSCM] - Safety Officer, Medical Monitor) will be provided with an individual password to access the IXRS menu that will enable them to unblind a subject's double-blind treatment allocation. This password must be kept confidential and not shared with any other persons. The IXRS will be able to identify the individual who has unblinded a subject's treatment allocation. The IXRS will be accessible at all times. If possible, Investigators are advised to contact the company or its representatives prior to unblinding the treatment allocation of subjects.

Under normal circumstances, the blinded treatment must not be revealed. In the case of a medical emergency, UCB or its representatives preferably should be contacted prior to any unblinding. The blind should be broken only if doing so will change the decision making as to the subject's treatment or clinical intervention. Any unblinding performed by the Investigator of the IMP must be documented and explained by the Investigator. If the blind is broken, the date, the reason for the breaking the blind, and person doing so must be recorded. UCB or its representatives must be notified immediately if the blind is broken.

In the event of an emergency, it will be possible to determine which treatment arm and dose the subject had been allocated to by calling the IXRS. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor (or equivalent) should be consulted prior to unblinding, whenever possible.

For the product and study information and emergency unblinding purposes, the Sponsor will provide each Investigator with an appropriate quantity of clinical study subject cards. Each

subject will be instructed to keep the card with him/her at all times. These subject cards will be written in the language of the subject. The Investigator will fill in each card with the details of his/her contact information (eg, Investigator stamp) and subject identifier. The card will be distributed to the subject at the time of informed consent.

The Clinical Project Manager (CPM) will be informed immediately via the IXRS when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the IMP performed by the Investigator must be recorded in the source documents and on the Study Termination CRF page.

7.10 Randomization and numbering of subjects

7.10.1 Interactive Response System

An IXRS is used for subject registration as well as randomization and treatment administration.

To enroll a subject, the Investigator must contact the IXRS and provide brief details of the subject to be enrolled. Each subject will be assigned a unique subject number. Enrolled subjects who withdraw from the study prior to randomization will retain their subject number without receiving a randomization number (ie, subject numbers will not be reassigned).

The IXRS will allocate kits of study medication at Weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50.

7.10.2 Randomization

Randomization will be stratified on:

- Region
- MRI/CRP classification

Subjects will be classified as MRI+/- depending on whether or not they have evidence of sacroiliitis on MRI at Screening based on the ASAS/OMERACT definition. Subjects will be classified as CRP+/- based on the CRP value obtained at the second Screening visit scheduled to occur 3 to 5 days prior to Baseline. Subjects will be categorized as CRP+ if their CRP value is above the level indicative of inflammatory disease at this visit. Otherwise, they will be considered CRP-. Based on these definitions, the stratification for MRI/CRP classification will have the following 3 levels:

- MRI+/CRP+
- MRI+/CRP-
- MRI-/CRP+

The IXRS will be designed to ensure that at least 20% of the randomized subjects belong to each of the 3 clinical subgroups above.

To randomize a subject, the Investigator must contact the IXRS and provide brief details of the subject that is to be randomized. The IXRS will automatically inform the Investigator of the subject's randomization number. Each subject will be assigned a unique randomization number. This randomization number will be required in all communications between the Investigator (or his/her designee) and the IXRS regarding a particular subject. The IXRS will allocate kit numbers to the subjects based on the randomization list over the course of the study.

Randomization numbers and kit numbers will be tracked via the IXRS and also will be required to be entered into the CRF.

Randomization schedules will be generated prior to start of the study. Subjects will be allocated to treatment in a 1:1 ratio (CZP 200mg: placebo).

8 STUDY PROCEDURES BY VISIT

Section 5.2 (Schedule of study assessments) provides a general overview of study assessments. A detailed listing of procedures to be undertaken at each visit is described below.

During the first 3 periods of the study the Investigator will assess the subjects over the entire study period of approximately 66 weeks including a FU Period of 8 weeks after the Week 52/WD visit. Visit windows of ±3 days on either side of the scheduled visit are permitted; however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±3 days is relative to Baseline and is applicable for all subsequent visits. Changes to the dosing schedule outside of the 3-day window must be discussed with the Medical Monitor and may result in subject withdrawal.

8.1 Screening visit (Week -6 to Day -1)

Prior to any study activities, subjects will be asked to read and sign an informed consent form that has been approved by an IEC/IRB and the Sponsor and which complies with regulatory requirements. Subjects will be given adequate time to consider any information concerning the study given to them by the Investigator or designee. As part of the informed consent process, subjects will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study.

Assessments at the Screening visit include:

- Confirm inclusion/exclusion criteria (to be performed within Weeks -6 and Day -1 and confirmed between Days -5 and -3 before Baseline)
- Confirm informed consent
- Demographic data (includes date of birth, gender, race/ethnicity)
- Significant past medical and procedure history and concomitant disease (includes allergy and any current symptoms) including axSpA history
- Vital signs (pulse rate, systolic and diastolic blood pressure, temperature, and respiratory rate)
- Hematology, biochemistry, and urine for clinical laboratory values (includes a serum pregnancy test for women of childbearing potential; testing to rule out hepatitis B surface antigen, antibodies to hepatitis C, and HIV; testing of CRP, HLA-B27, and abnormalities for estimated Glomerular Filtration Rate as measured by CKD-EPI will be performed)
- Physical examination (including weight)
- Chest x-ray to be done at Screening (unless a chest x-ray or computed tomography of the chest has been done within 3 months prior to the Screening visit)

- TB test: IGRA test (QuantiFERON test [or Elispot test when the QuantiFERON test is indicated but not available])
- TB evaluation questionnaire
- SI joint x-ray (centrally read). An SI joint x-ray performed ≤12 months prior to the Baseline visit maybe used as the Baseline assessment provided that the film can be submitted and meets the requirements for central reading.
- MRI (spine and SI joints, centrally read)
- BASMI and spinal mobility assessments
- BASDAI
- Prior and concomitant medication
- Contact the IXRS to indicate the subject has been screened

The period between the Screening and Baseline visits should not exceed 6 weeks. The Screening chest x-ray should be read by a radiologist/pulmonologist and must exclude evidence of TB. The qualifying CRP levels from the Screening visit will be used for the inclusion criteria review at Baseline.

One retest of CRP is mandatory during the Screening Period within 3 to 5 days before the Baseline visit in order to meet the inclusion criteria.

One rescreen is permitted for subjects with LTB. In this event, all Screening assessments must be repeated. Subjects are allowed to start the IMP after at least 4 weeks of prophylactic TB treatment (if compliant with the local regulations on initiation of biologic therapy in subjects with LTB) within the Screening Period. The subject is required to complete the full prophylactic treatment.

8.2 Baseline visit (Week 0)

Subjects agreeing to participate in the study, after giving signed informed consent, will have the following procedures performed/recorded prior to study drug administration:

- Review of inclusion/exclusion criteria. Note: The qualifying CRP levels from the Screening Period 3 to 5 days before Baseline will be used for the inclusion criteria review and for randomization stratification. The result of the centrally read MRI and X-ray must be available for the inclusion criteria review.
- Vital signs (pulse rate, systolic and diastolic blood pressure, temperature, and respiration rate)
- Blood samples (subjects should be encouraged to be under fasting conditions, the same condition [fasting or not fasting] should be applied at Week 52) will be collected for hematology and biochemistry analyses (biochemistry assessment will include the measurement of apolipoprotein (Apo) A1, ApoB, lipoprotein(a), and glycated hemoglobin [HbA1c])
- Urine will be collected for urinalysis and for a urine pregnancy test for women of childbearing potential

- Physical examination (including height and extra-articular assessments)
- TB questionnaire
- BASMI and spinal mobility
- BASDAI
- BASFI
- SF-36
- ASQoL
- MOS Sleep Scale
- EQ-5D
- MASES
- Total spinal pain NRS and nocturnal spinal pain NRS
- Swollen and tender joint counts
- PGADA
- PhGADA
- Productivity measures (WPS)
- Resources utilization
- Plasma for CZP concentration, anti-CZP antibodies, and biomarkers
- Genetics/epigenetics, if applicable
- Gene expression and proteomics, if applicable
- Concomitant medication
- AEs
- Contact IXRS to randomize subject and to obtain kit number
- Study drug administration (after all other visit assessments are completed and laboratory samples are drawn)

8.3 Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, and 50 (all visits ±3 days relative to Baseline)

Assessments at these visits include:

- Vital signs; pulse rate, systolic and diastolic blood pressures and temperature (respiration rate will be assessed in addition if the subject experiences an AE) (at all on-site visits except Week 1)
- Blood samples will be collected for hematology, biochemistry, and CRP (Weeks 2, 4, 8, 12, 24, and 36 only)

- CRP for the calculation of ASDAS (Weeks 16, 20, 28, 32, 40, 44, and 48)
- Urine will be collected for urinalysis (Weeks 2, 4, 8, 12, 24, and 36 only)
- Physical examination (Weeks 2, 4, 8, 12, 16, 24, and 36), including weight at Week 24
- Extra-articular assessments (Weeks 4, 12, 24, 36, and 48 only)
- TB questionnaire (Weeks 12, 24, and 36 only)
- MRI (spine and SI joints; Week 12 only)
- BASMI and spinal mobility (at all on-site visits except Weeks 6, 10, and 50)
- BASDAI (Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 only)
- BASFI (Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 only)
- SF-36 (Weeks 4, 12, 24, 36, and 48 only)
- ASQoL (Weeks 1, 2, 4, 12, 24, 36, and 48 only)
- MOS Sleep Scale (Weeks 4, 12, 24, 36, and 48 only)
- EQ-5D (Weeks 4, 12, 24, 36, and 48 only)
- MASES (Weeks 1, 2, 4, 8, 12, 16, 24, 32, 40, and 48 only)
- Total spinal pain NRS and nocturnal spinal pain NRS (Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 only)
- Swollen and tender joint counts (Weeks 4, 12, 24, and 36 only)
- PhGADA (Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 only)
- PGADA (Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 only)
- Productivity measures (WPS) (Weeks 4, 12, 24, 36, and 48 only)
- Resource utilization (Weeks 4, 12, 24, 36, and 48 only)
- Plasma for CZP concentration, anti-CZP antibodies, and biomarkers (Weeks 1, 2, 4, 12, 24, and 36 only)
- Genetics and epigenetics (Week 12 only), if applicable
- Gene expression and proteomics (Weeks 4 and 12), if applicable
- Concomitant medication
- AEs
- Contact IXRS to register the visit and obtain next kit number, where applicable (Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50)
- Study drug administration (after all other visit assessments are completed and laboratory samples are drawn) (all visits except Week 1)
- Subject training on self-injection (Weeks 10 and 12)

8.4 Every 4 weeks (± 3 days) during home injection period from Week 14 to Week 46 (Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46)

The following assessments are to be performed by telephone:

- Concomitant medication
- AEs

8.5 Week 52/WD (±3 days)

A subject is regarded to have completed the Double-Blind Period of the study if s/he completes the Week 52 assessments. Assessments at this visit include:

- Vital signs; pulse rate, systolic and diastolic blood pressure, and temperature (respiration rate will be assessed in addition if the subject experiences an AE)
- Blood samples (subjects should be encouraged to be under fasting conditions, the same condition [fasting or not fasting] should be applied at Week 52) will be collected for hematology, biochemistry, and CRP (biochemistry assessment will include the measurement of Apo A1, ApoB, lipoprotein(a), and HbA1c)
- Urine will be collected for urinalysis and for a urine pregnancy test for women of childbearing potential
- Physical examination (including weight)
- Extra-articular assessments
- Chest x-ray only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection
- TB test: IGRA test (QuantiFERON test [or Elispot test when QuantiFERON test is indicated but not available]) only for subjects who have not had a previously positive TB test result
- TB Questionnaire
- SI joint x-ray
- MRI for spine and SI joints (at Week 52/WD visit if previous MRI was performed more than 12 weeks prior to Week 52/WD visit)
- BASMI and spinal mobility
- BASDAI
- BASFI
- SF-36
- ASQoL
- EQ-5D
- MASES
- Total spinal pain NRS and nocturnal spinal pain NRS

- Swollen and tender joint counts
- PhGADA
- PGADA
- Productivity measures (WPS)
- Resources utilization
- Plasma for CZP concentration, anti-CZP antibodies, and biomarkers
- Gene expression and proteomics, if applicable
- Concomitant medication
- AEs
- Contact IXRS to indicate that subject has rolled over to the SFE Period or withdrawn from the study

8.6 SFE Period (Week 52 to Week 156)

All eligible subjects must complete the Week 52 visit assessments.

Eligible subjects are allowed to roll-over to the SFE-Period up to 3 months after completion of the Week 52 assessments.

Prior to rolling over to the SFE Period, subjects will be asked to read and sign a separate informed consent form.

Telephone contacts are upon the discretion of the Investigator. Starting at Week 56, and at the discretion of the Investigator, it is recommended to contact the subject by phone at least once in between the on-site visits.

Starting at Week 64, all subjects are to visit the site approximately every 12 weeks for assessments performed according to local standard medical practice, as needed, including:

- Document AEs (Note: any [possible] drug-related AE must be followed-up, at least by phone.)
- Contact IXRS
  - to register the visit and obtain next kit number at Weeks 54 and 56 for subjects receiving loading doses of study drug administration at the study site
  - to register the visit and obtain next kit number for subjects receiving study drug administration at the study site approximately Q12W during the remainder of the study
  - to indicate that subject has completed the SFE Period or withdrawn from the study (Week156/WD)

8.7 FU visit (8 weeks after the Week 52/WD visit [±3 days])

Subjects not participating in the SFE Period will attend a FU visit 8 weeks after the Week 52/WD visit (±3 days).

Assessments at this visit include:

- Vital signs; pulse rate, systolic and diastolic blood pressure, and temperature (respiration rate will be assessed in addition if the subject experiences an AE)
- Blood samples will be collected for hematology, biochemistry, CRP, and serum pregnancy test for women of childbearing potential
- Urine will be collected for urinalysis
- Physical examination
- Plasma for CZP concentration, anti CZP antibodies, and biomarkers
- Concomitant medication
- AEs
- Contact IXRS to indicate that subject has completed FU

8.8 Unscheduled visits

It is at the Investigator's discretion to initiate an Unscheduled Visit, if deemed necessary by the Investigator for the subject's safety and well-being. At this visit, any of the following or other assessments at the Investigator's discretion may be performed depending on the reason for the visit:

- Vital signs
- Blood samples for hematology, biochemistry, other testing such as for TB or CRP
- Urine for urinalysis and/or pregnancy testing (for women of childbearing potential)
- Physical examination
- Concomitant medication
- AEs
- TB questionnaire
- Contact IXRS to indicate that subject attended an unscheduled visit

8.9 Alternative visit schedules after subject discontinuation of the double-blind study treatment

Subjects who discontinue the double-blind study treatment and enter open-label treatment with CZP will be assessed 2 and 4 weeks after open-label CZP treatment has been initiated and every 12 weeks thereafter. Alternatively, subjects who discontinue the double-blind study treatment and receive other treatment (including biologics) will be assessed every 12 weeks after initiation of the other treatment. The alternative schedules for open-label CZP and other treatment can be found in Table 5–2 and Table 5–3 , respectively. In either alternative schedule, assessments

should be conducted until as close as possible to Week 52 (within ±4 weeks), where Week 52 is relative to the original randomization at Week 0. Subjects will then be invited to the final assessment visit at Week 52.

The following assessments will be performed for subjects who are treated with open-label CZP after discontinuation of the double-blind study treatment:

- Vital signs; pulse rate, systolic and diastolic blood pressure, and temperature (respiration rate will be assessed in addition if the subject experiences an AE) at wdt Weeks 0, 2, 4, 12, 24 (and every 12 weeks [Q12W]), 52, and FU (8 weeks after Week 52 visit)
- Blood samples will be collected for hematology, biochemistry, and CRP analyses, and urine will be collected for urinalysis at wdt Weeks 0, 12, 24 (and Q12W), 52 and FU (8 weeks after Week 52 visit)

  Note: Fasting blood samples will be collected for hematology, biochemistry, and CRP analyses at wdt Week 0 (biochemistry assessment will include the measurement of Apo A1, ApoB, lipoprotein(a), and HbA1c). At Week 52, the biochemistry assessment will include the measurement of HbA1c.
- Pregnancy test for women of childbearing potential at wdt Weeks 0, 52 (urine testing), and FU (serum testing)
- Physical examination at wdt Weeks 0, 4, 12, 24 (and Q12W), 52, and FU
- Extra-articular assessments at wdt Weeks 12, 24 (and Q12W), and 52
- TB test at wdt Week 52 only
- TB questionnaire at wdt Weeks 0, 12, 24 (and Q12W), and 52
- SF-36, AsQoL, MOS Sleep Scale, EQ-5D, and MASES at wdt Weeks 0, 12, 24 (and Q12W), and 52
- BASMI & spinal mobility, BASFI, total and nocturnal spinal pain, swollen and tender joint counts, BASDI, Patient's Global assessment, and Investigator's AS assessment at wdt Weeks 0, 4, 12, 24 (and Q12W), and 52
- Plasma for CZP concentration, anti-CZP antibodies, and for biomarkers at wdt Weeks 0, 4, 12, 24 (and Q12W), 52, and FU
- Gene expression and proteomics at wdt Week 52 only
- Concomitant medication at wdt Weeks 0, 2, 4, 12, 24 (and Q12W), 52, and FU
- AEs at wdt Weeks 0, 2, 4, 12, 24 (and Q12W), 52, and FU
- IXRS (for treatment assignment) at wdt Weeks 0, 2, 4, 12, 24 (and Q12W), 52, and FU
- CZP administration at wdt Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and every 2 weeks thereafter, until Week 52. Loading dose of CZP 400mg at Weeks 0, 2, and 4 must be administered by dedicated site-staff
- Telephone contact will occur every 4 weeks after the on-site visit at the discretion of the investigator

The following assessments will be applied for subjects who receive an alternative study assessment with other treatment (including biologics) after discontinuation of the double-blind study treatment:

- Blood samples will be collected for hematology and biochemistry analyses, and urine will be collected for urinalysis at wdt Week 0. C-reactive protein analyses will be performed at wdt Weeks 0, 12, 52, and FU

  Note: Biochemistry assessment will include the measurement of HbA1c at wdt Week 0
- Physical examination at wdt Week 0 and FU.
- BASDAI, BASFI, total and nocturnal spinal pain, Patient's Global assessment, and Investigator's AS assessment at wdt Weeks 0, 12, and 52
- Swollen and tender joint counts at wdt Week 52 only
- Plasma for CZP concentration, anti-CZP antibodies, and for biomarkers at wdt Weeks 0, 12, and FU
- Concomitant medication at wdt Weeks 0, 12, 24 (and Q12W), 52, and FU
- AEs and IXRS (for the registration of visits) at wdt Week 0, 12, 24 (and Q12W), 52, and FU
- Other treatment administration at wdt Week 0. For Week 12 and 24 (and Q12W) the regimen of the particular medicine should be followed. If the Investigator choses to withdraw the subject, the local guidelines on initiation and monitoring of the particular treatment should be followed.
- Telephone contact will occur every 4 weeks after the on-site visit at the discretion of the investigator

9 ASSESSMENT OF EFFICACY

Most of these tools have been used in AS studies but early data support their use in axSpA as well (Barkham et al, 2009; Haibel et al, 2008).

9.1 Assessment of efficacy variables

9.1.1 ASDAS

The ASDAS is comprised of a number of assessments which are scored by the subject and physician and multiplied by a proven formula (van der Heijde et al, 2009) as listed:

0.121 x Back pain (BASDAI Q2 result, see Section 9.1.5)

0.058 x Duration of morning stiffness (BASDAI Q6 result)

0.110 x PGADA (see Section 9.1.13)

0.073 x Peripheral pain/swelling (BASDAI Q3 result)

0.579 x (natural logarithm of the CRP [mg/L] + 1)

Back pain, PGADA, duration of morning stiffness, peripheral pain/swelling and fatigue are all assessed on a numerical scale (0 to 10 units) (Lukas et al, 2009).

The variables related to ASDAS disease activity are defined as follows:

- ASDAS-Inactive Disease (ASDAS-ID): ASDAS <1.3
- ASDAS-Moderate Disease (ASDAS-MD): ASDAS ≥1.3, <2.1
- ASDAS-High Disease Activity (ASDAS-HD): ASDAS ≥2.1, ≤3.5
- ASDAS-very High Disease Activity (ASDAS-vHD): ASDAS >3.5

The variables related to ASDAS improvement are defined as follows:

- ASDAS-Clinically Important Improvement (ASDAS-CII): ASDAS reduction (improvement) of ≥1.1 relative to Baseline
- ASDAS-Major Improvement (ASDAS-MI): ASDAS reduction (improvement) of ≥2.0 relative to Baseline

The ASDAS will be calculated at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32 36, 40, 44, 48, and 52/WD.

9.1.2 ASAS20, 40, ASAS 5/6 response, and ASAS partial remission

The ASAS20 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:

- PGADA (see Section 9.1.13)
- Pain assessment (the total spinal pain NRS score)
- Function (represented by BASFI, Section 9.1.6)
- Inflammation (the mean of the BASDAI questions 5 and 6, [see Section 9.1.5] 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 ASAS criteria for 40% improvement are defined as relative improvements of at least 40%, and absolute improvement of at least 2 units on a 0 to 10 NRS in at least 3 of the 4 domains and no worsening at all in the remaining domain.

The ASAS 5/6 response is defined as at least 20% improvement in 5 of 6 domains, including spinal mobility (lateral spinal flexion) and CRP as more objective measures (Brandt et al, 2004).

The ASAS partial remission response is defined as a score of ≤2 units on a 0 to 10 unit scale in all 4 domains listed above for ASAS20.

The ASAS variables will be calculated at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52/WD.

9.1.3 ASAS-NSAID score

The ASAS-NSAID score is a tool that has been developed to measure the magnitude of NSAID intake during clinical studies (Dougados et al, 2011). In order to calculate the ASAS-NSAID score, the following information will be collected:

- Has there been NSAID intake since last visit?

- NSAID name
- Average daily intake (mg)
- Days with intake
  - <1 day/week
  - 1 to 3 days/week
  - 3 to 5 days/week
  - ≥5 days/week
  - Every day
- Starting date
- End date (or ongoing)

The general formula for calculation is as follows:

- (equivalent NSAID score) × (days of intake during period of interest) × (days per week)/(period of interest in days)

Each of the components of the above calculation is described below:

- Equivalent NSAID score: This is reported in terms of NSAID equivalent dose in mg/day on a 0 to 100 scale where the diclofenac 150mg equivalent is set to 100. An NSAID equivalence table was developed based on a survey of ASAS members. The table including the consensus equivalence score for various NSAIDs can be found in the Statistical Analysis Plan (SAP).
- Days of intake during period of interest: Equivalent to the total number of days covered during the period that is being measured.
- Days per week: Proportion of days per week when the NSAID is taken. This is collected in the categories described in the days with intake category listed above. Each category corresponds to a score as follows (score in parentheses):
  - Every day (7/7)
  - ≥5 days/week (6/7)
  - 3 to 5 days/week (4/7)
  - 1 to 3 days/week (2/7)
  - <1 day/week (0.5/7)
  - No NSAID intake (0)
- Period of interest in days: Refers to the number of days covered for a given NSAID. If only 1 NSAID was taken during the period of interest, this will be the same as days of intake during period of interest.

Dougados et al 2011 provided the following example. If during a period of interest (between 2 visits) of 6 months, the subject has taken piroxicam 20mg during 4 months and if during this 4 month-period he has taken piroxicam 3 to 5 days per week the calculation is as follows:

- 100 (20mg piroxicam score) × 120 (4 months) × 4/7 (3 to 5 days/week)/180 (6 months) = 38.1

If the subject has used 10mg piroxicam during the remaining 2 months on 2 days a week, the NSAID score for this period is:

- 50 (10mg piroxicam score) ×60 (2 months) × 2/7 (1 to 3 days/week)/180 (6 months) = 4.8

In this example the total score for the 6-month period is 42.9 (38.1 plus 4.8).

9.1.4 ASQoL

The ASQoL, a validated disease-specific 18-item questionnaire, has been developed specifically for measuring HRQoL in subjects with AS (Doward et al, 2003). The ASQoL has been used and has shown to be responsive in axSpA (Barkham et al, 2009; Haibel et al, 2008). The ASQoL score ranges from 0 to 18 with higher score indicating worse HRQoL. A change of 1.8 points, which represents 10% of the possible score range, has been used as the minimal clinically important difference (MCID) criteria to guide the interpretation of ASQoL score changes in previous trials with a TNFi (van der Heijde et al, 2009; Davis et al, 2007). A change in ASQoL score of 2 points (ie, 10% of the total score range) will be used as the MCID to guide the interpretation of ASQoL score changes (see Appendix 18.4).

The ASQoL assessments per visit are described in Table 5–1 and Table 5–2.

9.1.5 BASDAI

The most common instrument used to measure the disease activity of AS from the subject's perspective is the BASDAI (Garrett et al, 1994). 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 (van Tubergen et al, 2015). The final BASDAI score ranges from 0 to 10, with lower scores indicating lower disease activity. The MCID used to interpret scores is 10mm on a VAS or 22.5% of the Baseline score (Pavy et al, 2005). An MCID of 1 unit will be selected for the NRS version (see Appendix 18.5).

The BASDAI 50 is defined as an improvement of at least 50% in the BASDAI response.

The BASDAI is calculated as follows:

$$\frac{Q1 + Q2 + Q3 + Q4 + \left(\frac{Q5+Q6}{2}\right)}{5}$$

Fatigue item of the BASDAI

Fatigue as a major symptom of AS can effectively be measured with single-item questions such as the BASDAI item (van Tubergen et al, 2002b). This item has shown moderate to good reliability and responsiveness (van Tubergen et al, 2002b). The same MCID will be used for the fatigue item of the BASDAI as for the total BASDAI score, ie, a change of 1 unit on the NRS.

The BASDAI assessments per visit are described in the schedule of study assessments Table 5–1, Table 5–2, and Table 5–3.

9.1.6 BASFI

The BASFI is a validated disease-specific instrument for assessing physical function (van der Heijde et al, 2005; Calin et al, 1994). The BASFI comprises 10 items relating to the past week. The NRS version will be used for the answering options of each item on a scale of 0 ("Easy") to 10 ("Impossible") (van Tubergen et al, 2015 and van Tubergen et al, 2002a). The BASFI is the mean of the 10 scores such that the total score ranges from 0 to 10, with lower scores indicating better physical function. The MCID used to interpret scores is 7mm on a 0 to 100mm VAS or 17.5% of the Baseline score (Pavy et al, 2005); an MCID of 1 unit will be used for the NRS version (see Appendix 18.6).

The BASFI assessments per visit are described in Table 5–1, Table 5–2, and Table 5–3.

9.1.7 BASMI

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

The BASMI assessments per visit are described in Table 5–1 and Table 5–2.

9.1.8 Enthesitis (MASES)

The MASES is an index that measures the severity (ie, intensity and extent) of enthesitis through the assessment of 13 entheses (bilateral costochondral 1, costochondral 7, anterior superior iliac spine, posterior iliac spine, iliac crest and proximal insertion of the Achilles tendon sites, and the fifth lumbar vertebral body spinous process) (Heuft-Dorenbosch et al, 2003) each scored as 0 or 1 and then summed for a possible score of 0 to 13.

Enthesitis assessments per visit are described in Table 5–1 and Table 5–2.

9.1.9 Extra-articular assessments

The evolution of associated nonmusculoskeletal features including IBD, psoriasis and uveitis (including their severity) and flare rate will be assessed as described Table 5–1 and Table 5–2.

9.1.10 Health status (EQ-5D)

The EQ-5D is comprised of a 5-item health status measures and a VAS. Each of the 5 health states is divided into 3 levels: no problem, some or moderate problems and extreme problems and is scored as 1, 2, and 3, respectively. The EQ-5D VAS records the respondent's self-rated health status on a vertical 20 cm scale, 0 to 100 graduated (0=worst imaginable health status, 100=best imaginable health status) (see Appendix 18.7).

This instrument is to be completed by the subject as described in Table 5–1 and Table 5–2.

9.1.11 MOS Sleep Scale

The MOS Sleep Scale is a validated generic self-administered scale measuring specific aspects of sleep. The frequency with which each problem has been experienced during the previous 4 weeks is rated on a 5-point scale ranging from "none of the time" to "all of the time," except

sleep quantity, which is reported in hours. All scores are transformed linearly to range from 0 to 100, again with the exception of the sleep quantity subscale, which is scored in hours. Higher scores indicate more of the attribute implied by the scale name (eg, more sleep disturbance, more adequate sleep, and greater sleep quantity). The psychometric properties of the MOS Sleep Scale have been found to be satisfactory by Hayes and colleagues (Hays et al, 2005). The domains of interest for this study are the Sleep Disturbance and the Sleep Problems Index II domains. The MCID for the Sleep Problems Index II is 6 points on a 0 to 100 scale (Wells et al, 2007) (see Appendix 18.8).

Subjects will be asked to complete the MOS Sleep Scale as described in Table 5–1 and Table 5–2.

9.1.12 MRI assessments

Magnetic Resonance Imaging according to the ASAS/OMERACT definition is the presence of bone marrow oedema (BMO) or osteitis highly suggestive of SpA that is located in the typical anatomical areas (subchondral or periarticular bone marrow). There must be either more than 1 BMO lesion on 1 slice or a lesion that is present on at least 2 consecutive slices (Rudwaleit et al, 2009d). In practice this is very similar to the SI joint SPARCC score ≥2 definition of MRI that requires at least 2 BMO lesions to be present. A recent paper showed that the sensitivity and specificity of the ASAS/OMERACT and SI joint SPARCC score ≥2 definitions of MRI positive were identical (sensitivity 0.80, specificity 0.76) (Weber et al, 2014). The Berlin modification of the ASspiMRI-a is a scoring system with a concentration on short-tau-inversion recovery (STIR) sequences without other fat saturation techniques (Braun and Baraliakos, 2011; Lukas et al, 2007; Braun and van der Heijde, 2002; Braun et al, 2003). This scoring method quantifies changes in 23 vertebral units (VU) of the spine (from C2 to S1). A VU is defined as the region between 2 virtual lines through the middle of each vertebra. Active inflammation is scored by grading the degree of BMO from 0 to 3 in 1 dimension on 1 or more consecutive slices that represent the highest level of inflammation in a particular VU. Total spine ASspiMRI-a score in the Berlin modification can range from 0 to 69. In addition to the method mentioned above, MRIs may be evaluated using other reading criteria.

Magnetic resonance imaging of the spine and SI joints will be performed at Screening and at the Week 12 and at the Week 52/WD visits if MRI was performed more than 12 weeks prior to Week 52/WD. Magnetic resonance images will be assessed centrally and scoring will be done by 2 independent readers, who are blinded to both the order of the scans and to the treatment group, using a previously reported scoring system.

9.1.13 PGADA (NRS)

Subjects will score their global assessment of their disease activity in response to the question "How active was your spondylitis on average during the last week?" using a NRS where 0 is "not active" and 10 is "very active" (van Tubergen et al, 2015) (see Appendix 18.9).

The PGADA assessments per visit are described in Table 5–1, Table 5–2, and Table 5–3.

9.1.14 PhGADA

The Investigator will assess the overall status of the subject with respect to the axSpA signs and symptoms and the functional capacity of the subject using a VAS where 0 is "very good,

asymptomatic and no limitation of normal activities" and 100 is "very poor, very severe symptoms which are intolerable and inability to carry out all normal activities."

This assessment by the Investigator should be blinded.

The PhGADA will be completed as described in Table 5–1, Table 5–2, and Table 5–3.

9.1.15 Productivity measures (Work Productivity Survey)

The WPS is an instrument used to assess productivity at work and within the home. The WPS has been found to be valid, reliable, and responsive to clinical changes in RA, PsA, and axSpA subjects (Osterhaus and Purcaru, 2014).

Site personnel should obtain information from the subject in order to complete this survey. The WPS is a 9-question instrument used to assess the impact of arthritis on productivity within and outside the home during the preceding 4 weeks. [redacted] on a 0 to 10 scale (0=no interference; 10=complete interference). [redacted] on a 0 to 10 scale (0=no interference; 10=complete interference).

The WPS assessments per visit are described in Table 5–1.

9.1.16 Resources utilization

Study-specific questionnaires (standard CRF modules) will be used to capture data regarding resources utilization during the study, ie:

- Concomitant medical procedures
- Health care provider consultations not foreseen by the protocol
- Hospitalizations/emergency room visit

Site personnel should obtain information from the subject and also corroborate data with known AEs and SAEs in order to complete this survey as described in Table 5–1. The recall period for the questionnaire will be the previous 4 weeks.

9.1.17 SF-36

The SF-36 (version 2, standard recall) is a 36-item generic HRQoL instrument that uses a recall period of 4 weeks. Items are grouped into 8 domains as follows: Physical Functioning (10 items), Role Physical (4 items), Bodily Pain (2 items), General Health (5 items),Vitality (4 items), Social Functioning (2 items), Role Emotional (3 items), Mental Health (5 items), and 1 item for perceived stability or change in health (Health Transition) during the last year. The concepts represented by these domains contribute to physical, mental, and social aspects of HRQoL.

In addition to domain scores, the PCS and MCS scores are calculated from the 8 domains (excluding the Health Transition item). Component scores appreciate the impact of each domain on physical and mental health status (Ware et al, 1994). Each of the 8 domain scores and the component summary scores range from 0 to 100, with a higher score indicating a better health status. The 2 component summary scores are standardized with a mean of 50 and a standard deviation (SD) of 10 in the general USA population. The MCIDs for SF-36 domains and component summaries are 5 and 2.5 points, respectively (Strand et al, 2005) (see Appendix 18.10).

The SF-36 has been used and has shown to be responsive in axSpA (Haibel et al, 2008) and is also validated (van Tubergen et al, 2015). The SF-36 will be administered per visit as described in Table 5–1 and Table 5–2.

9.1.18 Spinal mobility

In addition to the assessments performed for the BASMI, additional spinal mobility assessments include:

- Occiput to wall distance
- Chest expansion

Spinal mobility will be assessed as described in Table 5–1 and Table 5–2.

9.1.19 Swollen and tender joint counts (44 joints evaluation)

The following 44 joints are to be examined for swelling and tenderness by the Principal Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. Preferably the same assessor should evaluate the subject at each arthritis assessment.

Upper body (4) – bilateral sternoclavicular, and acromioclavicular joints

Upper extremity (26) – bilateral shoulders, elbows, wrists (includes radiocarpal, carpal and carpometacarpal bones considered as a single unit), metacarpophalangeals (MCPs) I, II, III, IV, and V, and thumb interphalangeals (IPs), and proximal IPs (PIPs) II, III, IV, and V

Lower extremity (14) – bilateral knees, ankles, and metatarsophalangeals (I, II, III, IV, and V)

The assessment for swelling and tenderness is made on 44 joints from the above list. Artificial and ankylosed joints are excluded from swelling and tenderness assessments.

The assessments per visit are described in Table 5–1 and Table 5–2.

Table 9–1: Swelling and tenderness grading

Grade	Swelling response (44)	Tenderness response (44)
0	None	None
1	Swelling present	Tenderness present

9.1.20 Total and nocturnal spinal pain NRS

The pain experienced by AS subjects is adequately measured by 2 separate questions: 1) total pain in the spine due to AS (ie, "How much pain of your spine due to spondylitis do you have?"); and 2) pain in the spine at night due to AS (ie, "How much pain of your spine due to spondylitis do you have at night?") (Sieper et al, 2009; van der Heijde et al, 2005; CPMP/EWP/556/95). Usually, a 10% difference (ie, a 1 point difference on a NRS ranging from 0 to 10) is considered the MCID used to interpret scores (Dworkin et al, 2008). Pain experienced by axSpA subjects has also been measured with this assessment (Haibel et al, 2008) and is validated (van Tubergen et al, 2015) (see Appendix 18.11).

The pain NRS assessments per visit are described in Table 5–1, Table 5–2, and Table 5–3.

10 ASSESSMENT OF PHARMACOKINETICS, EXPLORATORY BIOMARKERS, AND PHARMACOGENOMICS VARIABLES

Plasma samples for the measurement of CZP concentrations will be taken at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52/WD, and at the FU visit (8 weeks after the Week 52/WD visit). These plasma samples may be used additionally for analyses of CZP and its constituent moieties using alternative methods and the results of those analyses may be reported separately.

These plasma samples may be used for possible analyses of exploratory biomarkers which might include, but are not limited to: MMP-3, BMP-2, -4 and -7, WNT1, WISP, Gremlin, DKK1, Sclerostin, Hedgehog proteins (Shh, Ihh, Dhh), Collagen turnover/cleavage products, collagen type X, VEGF, citrullinated vimentin fragments, cytokines: IL13, IL17 A and F, IL23, IL34, (TGF-β, M-CSF, GM-CSF, CSF-1, sCSF1r levels. The results of the analyses of CZP and its constituent moieties from alternative methods may be reported separately.

For subjects participating in the optional substudy, blood samples will be drawn for possible genetics/epigenetics, genomic, proteomics and metabolomic analysis at Baseline and Week 12, and for genomic, proteomics, and metabolomic analysis only, at Week 4 and Week 52/WD to enable exploratory evaluation of biomarkers relative to drug treatment, disease biology and inflammatory and immune response processes.

Samples will be moved from the Central Laboratory (ACM) at the end of the study to a long-term storage facility - BioStorage Technologies, GmbH - and will be stored at -80°C at a central biorepository for up to 20 years.

11 ASSESSMENT OF IMMUNOGENICITY VARIABLES

Plasma samples for the measurement of anti-CZP antibodies and potentially neutralizing antibodies will be taken at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52/WD, and the FU visit (8 weeks after the Week 52/WD visit).

The sampling, handling, and shipment of samples will be performed as detailed in the Laboratory Manual.

12 ASSESSMENT OF SAFETY

12.1 Adverse events

12.1.1 Definition of adverse event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

If a surgical procedure is performed during the study participation, the underlying condition should be reported as the AE (eg, "appendicitis" is the AE resulting in appendectomy).

The following laboratory values and physical findings are also to be considered AEs:

- Laboratory value(s) that are out of reference range AND of clinical relevance, excluding Screening values
- Laboratory value(s) that change from a subject's Baseline AND are of clinical relevance
- Pre-existing physical findings (including vital sign measurements) that worsen compared with Baseline AND that are "clinically important"

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after signing the informed consent form), including any Screening and FU Periods required by the protocol, must be reported in the CRF even if no IMP was administered but specific study procedures were conducted. This includes all AEs not present prior to the Screening visit and all AEs which recurred or worsened after the Screening visit.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or the Baseline Period.

12.1.2 Procedures for reporting and recording adverse events

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the Investigator should review any self assessment procedures (eg, questionnaires) employed in the study.

12.1.3 Description of adverse events

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The CRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event CRF (including judgment of relationship to study drug) are described in the CRF Completion Guidelines.

12.1.4 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

If an AE is still ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the Investigator must provide a justification. The follow up will usually be continued for 70 days after the subject has discontinued his/her IMP.

12.1.5 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first AE and AE verbatim term repeated including worsening, so that the repeated AE can be easily identified as the worsening of the first one

12.1.6 Pregnancy

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately notify UCB's Drug Safety (DS) department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as the pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an Early Withdrawal Visit.
- The subject should immediately stop the intake of the IMP.
- A FU visit should be scheduled 8 weeks after the Week 52/WD visit.

The Investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form upon which the Investigator has to report the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the Investigator and filed at the site. UCB's DS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/CRO contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's DS department (for contact details see Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's DS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, therapeutic abortion, and unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE report form.

Should a subject become pregnant while participating in the study, the subject may be offered the option to enroll in a separate observational pregnancy follow-up study sponsored by UCB and conducted independently from study AS0006. If the study is available locally, the AS0006 Principal Investigator will be provided with the locally approved information about the observational pregnancy follow-up study to inform the subject at the time the pregnancy is reported. Participation in this separate study will be voluntary and will not impact therapeutic management of the subject nor interfere with termination and follow-up procedures as described in study protocol AS0006.

12.1.7 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the appropriate CRF module and drug accountability forms. Any SAE or nonserious AE associated with excessive dosing must be followed as any other serious or nonserious AE. These events may be symptomatic, in that the excessive dosing results in clinical signs and symptoms, or the excessive intake may itself be a symptom.

12.1.8 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the DS representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

12.2 Serious adverse events

12.2.1 Definition of serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- An important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious.
  Examples of important medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, infections that require treatment with parenteral antibiotics or the development of drug dependency or drug abuse.

  Confirmed active TB is an SAE and must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirements until such time as the TB infection resolves.
- Initial inpatient hospitalization or prolongation of hospitalization

  A subject admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious (eg, life-threatening adverse experience, important medical event).

  Hospitalizations for reasons not associated with the occurrence of an AE (eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner) do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.

  Hospitalization for diagnostic or therapeutic procedures in the absence of any associated AE will not be considered as an SAE, except when otherwise required by regulatory authorities.

If a hospitalization is planned prior to the subject receiving the first dose of IMP (at Week 0), it will not be classified as either an AE or SAE. This also applies to a scheduled elective surgery where no AE is present. A noncomplicated, preplanned elective surgery will not be considered an AE or SAE even if it involves hospitalization. However, if a hospitalization is unplanned or is a result of an AE, this will be considered to be an SAE.

12.2.2 Procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

It is important for the Investigator, when completing the SAE report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE report form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each subject (which is usually the FU visit), and to also inform participating subjects of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the current version of the CZP Investigator Brochure (IB).

12.2.3 Follow up of serious adverse events

An SAE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

Information on SAEs obtained after clinical database lock will be captured through the DS database without limitation of time.

12.3 Adverse events of interest

An AE of interest is any AE which is listed in the European Risk Management Plan, or meets another commitment requiring nonstandard expedited reporting, even if the AE does not fulfill

the expedited reporting criteria of "serious," "unexpected," and "associated with the use of the drug." Adverse events of interest include:

- Serious infections including opportunistic infections
- Malignancies including lymphoma
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia
- Serious bleeding events
- Lupus and lupus-like illness
- Serious skin reactions (eg., Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

Note : Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

12.4 Immediate reporting of adverse events

The following AEs must be reported immediately:

- SAE: AE that the Investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of interest (see Section 12.3)

12.5 Laboratory measurements

Hematology, biochemistry, urinalysis, and CRP samples will be taken at Screening, Baseline, Weeks 2, 4, 8, 12, 24, 36, 52/WD, and at the FU visit (8 weeks after the Week 52/WD visit). Testing to rule out hepatitis B, hepatitis C, and HIV will be performed at Screening as well as the HLA-B27 antigen determination. Subjects will be encouraged to be in fasting condition at Baseline and at Week 52/WD or at the time the subject shifts to alternative treatment, for Apo A1, ApoB, and lipoprotein(a) assessments.

The urinalysis will be performed with a dipstick, and in case of a positive outcome, on a clean catch urine sample sent to the central laboratory for analysis.

The central laboratory will analyze and assess blood and urine samples for the following (except where indicated):

Table 12–1: Laboratory measurements up to Week 52 (including the FU visit (8 weeks after the Week 52/WD visit)

Hematology	Serum biochemistry	Urinalysis	Others
Red blood cells	Sodium	pH	
Hemoglobin	Potassium	Protein	Hepatitis B surface antigen
Hematocrit	Chloride	Glucose	Antibodies to hepatitis C
Platelets	Bicarbonate	Blood	Antibodies to HIV
White blood cells	Total calcium	Esterase	HLA-B27
Neutrophils	Inorganic phosphorus		
Lymphocytes	CRP		
Monocytes	Creatine phosphokinase[a]		
Eosinophils	Glucose	Microscopy (WBC, RBC, casts, crystals, bacteria) (Microscopy will be performed only when there are abnormalities on dipstick)	
Basophils	Creatinine	Urine-sample to be collected for central-laboratory analysis only when there are abnormalities on dipstick	
	Uric acid		
	Urea		
	Total protein		
	Albumin		
	Alkaline phosphatase		
	Aspartate aminotransferase		
	Alanine aminotransferase		

Table 12–1: Laboratory measurements up to Week 52 (including the FU visit (8 weeks after the Week 52/WD visit)

Hematology	Serum biochemistry	Urinalysis	Others
	Bilirubin		
	Total cholesterol		
	HDL[b]		
	LDL[b]		
	HbA1c[c]		
	Apo A1		
	ApoB		
	Lipoprotein(a)		

Apo=Apolipoprotein; CRP=C-reactive protein; FU=Follow-Up; HbA1c=glycated hemoglobin; HDL=high density lipoprotein; HIV=human immunodeficiency virus; HLA-B27=human leukocyte antigen B27; LDL= low-density lipoprotein; RBC=red blood cells; WBC=white blood cells; ULN=upper limit of normal

[a] Creatine phosphokinase subtypes (CK-MM; CK-MB; and CK-BB) are required if the creatine phosphokinase measurement is >2 ULN.

[b] HDL and LDL are to be measured every 6 months and at the time the subject shifts to open-label CZP.

[c] HbA1c is to be measure at Baseline and Week 52/WD or at the time the subject shifts to open-label CZP.

For subjects participating in the SFE Period after Week 52, it is recommended that laboratory assessments be performed at the local laboratory at the discretion of the Investigator according to local standard medical practice to evaluate potential AEs.

12.6 Other safety measurements

12.6.1 Pregnancy testing

Pregnancy testing must be carried out for women of childbearing potential and will consist of serum testing at Screening and FU and urine testing (dipstick) at Baseline, at wdt Week 0 of the alternative study assessment (for subjects administering either open-label CZP or alternative treatment), and at Week 52/WD.

For subjects participating in the SFE Period after Week 52, it is recommended that pregnancy testing be performed according to local standard medical practice.

12.6.2 Physical assessments

Physical examination will be performed at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 24, 36, 52/WD, and at the FU visit (8 weeks after the Week 52/WD visit for subjects not participating in the SFE Period). It is recommended that physical examinations be performed according to local standard medical practice for subjects participating in the SFE Period after Week 52,

Physical examination findings will be recorded in the CRF only at Screening. Clinically important abnormal changes in subsequent physical examinations will be recorded as AEs. Physical examinations must be documented in source documentation.

The following body systems will be examined:

- General Appearance
- Ear, nose and throat
- Eyes
- Hair and skin
- Respiratory
- Cardiovascular
- Gastrointestinal
- Musculoskeletal
- Hepatic
- Neurological (including limb reflexes)
- Mental Status

In addition, the TB signs and symptoms will be assessed at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 24, 36, completion at Week 52/WD visit and FU (8 weeks after the Week 52/WD visit for subjects not participating in the SFE Period).

Weight is to be measured at Screening, Week 24, and at completion at Week 52/WD. Height will be measured at the Baseline visit only.

12.6.3 Assessment and management of TB and TB risk factors

As TNFi are known to be associated with significant risk of reactivation of LTB, appropriate rigorous precautions are being taken within the protocol to address this (see Section 6.2 [Exclusion Criterion 16] and Section 6.3 [Withdrawal Criterion 6]).

Signs and Symptoms

The Investigator should consider all potential sites of infection when assessing for TB during the subject's history and the physical examination, and other evaluations. Sites commonly infected by TB include: the lungs, larynx, lymph glands, pleura, gastrointestinal system, genito-urinary tract (including renal), bones and joints, meninges, peritoneum, pericardium, and skin. This is not an exhaustive list and unusual presentations and areas of involvement should always be considered.

Common symptoms that the subject may present with include cough, blood in sputum, night sweats, lymphadenitis, joint pain/swelling, spinal deformity, headache/confusion, abdominal pain mimicking IBD, frequent or painful urination, scrotal mass in men and pelvic inflammatory disease in women as well as other symptoms, or nonspecific symptoms. This is not an exhaustive list and unusual presentations should always be considered.

The subject may present an absence of signs, symptoms (ie, evidence of organ-specific involvement), or physical findings suggestive of TB infection with a positive IGRA test (or 2 indeterminate IGRA test results) and a chest x-ray (or other imaging) without evidence of TB infection. If the result of the IGRA test is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be randomized to study medication without further evaluation, treatment, and discussion with Study Physician, if LTB infection is identified. (If active TB is identified, subject must undergo appropriate study-specified withdrawal procedures.) The retest must be done during the protocol-defined Screening window.

Note: If available, respiratory or other specimens must also be smear and culture negative for TB (CDC diagnosis of LTB infection [http://www.cdc.gov/TB/topic/testing/default.htm]).

Test Conversion

Tuberculosis test conversion is defined as a positive result (IGRA) for the current test but previous test results were negative (IGRA). All subjects with TB test conversion must immediately stop study drug administration. In case of a TB test conversion, the subject must be considered as having either a suspected new LTB or an active TB infection and be promptly referred to an appropriate specialist (ie, pulmonologist, infectious disease specialist) must be consulted for further evaluation. If test conversion indicates LTB infection, active TB, or nonmycobacterial TB infection then per UCB TB working instructions, TB test conversion (confirmed) should be classified as due to LTB infection, active TB infection, or NTMB infection. Additional assessments (eg, blood tests or IGRA test, chest x-rays or other imaging) should be performed as medically indicated.

Latent TB

In case the evaluation by the appropriate specialist indicates a new LTB infection, a prophylactic TB treatment (as described in Section 6.2, Exclusion Criterion 16) should be initiated and study medication can be continued no sooner than 4 weeks after start of prophylactic TB treatment, if it is deemed likely that prophylactic TB treatment is continued to completion by the Investigator.

If prophylaxis is not initiated, the subject must to be withdrawn.

Every action should be discussed in advance with the Medical Monitor. Latent TB must be reported as an SAE.

Active TB/NTMB

Subjects who develop active TB or NTMB infection during the study (conversion demonstrated by IGRA) must be immediately discontinued from study medication, and a withdrawal visit must be scheduled as soon as possible, but not later than the next regular visit. The subject should be encouraged to keep the FU visit (8 weeks after the Week 52/WD visit for subjects not participating in the SFE Period). The TB must be documented as an SAE. Treatment for TB should be started based on local guidelines.

Note that subjects with history of or active NTMB infection are excluded from the study regardless of prior or current therapy.

Confirmed active TB is an SAE and an adverse event of special interest (AESI) and must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting

requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirement until such time as the TB infection resolves.

Subjects who prematurely discontinue treatment for LTB, or, in the opinion of the Investigator or Sponsor, are noncompliant with anti-TB therapy must discontinue further use of study medication and be immediately withdrawn. Once withdrawn from study treatment, subjects not participating in the SFE Period should return for the Week 52/WD visit, complete all Week 52/WD assessments, and complete a FU visit (8 weeks after the Week 52/WD visit).

12.6.3.1 Tuberculosis assessments

During conduct of the study the TB assessment by IGRA will be performed at Screening and should be repeated at Week 52/WD for all subjects not participating in the SFE Period. It is recommended that TB testing be performed according to local standard medical practice during the SFE Period.

The test results will be reported as positive, negative, or indeterminate and must be reviewed by an experienced TB specialist, radiologist, or a pulmonologist. If the assessment by IGRA is positive or indeterminate on retest for subjects who were previously negative at Screening and not treated for LTB, the subject may not continue study treatment without further evaluation by a TB specialist, prophylactic TB treatment, and discussion with the Medical Monitor, if LTB infection is identified. If active TB is identified, subject must undergo appropriate study specified withdrawal procedures. The retest must be done during the protocol-defined Screening window.

12.6.3.2 Chest x-ray

A plain posteroanterior chest x-ray must be done at Screening unless a chest x-ray (or a computed tomography of the chest) has been done within 3 months prior to the Screening visit. The chest x-ray must be clear of signs of TB infection (previous or current) before first study drug administration. For subjects not participating in the SFE Period the chest x-ray will be repeated at Week 52/WD visit (if chest x-ray was performed more than 12 weeks prior to Week 52/WD visit), only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). It is recommended that the chest x-ray be repeated for subjects participating in the SFE Period, if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

The chest x-ray (or, if done, the computed tomography of the chest) must be negative for TB infection as determined by a qualified radiologist and/ or pulmonary physician. Any new clinically significant findings post-Baseline during physical exam or on chest x-ray must be documented in the source documents and CRF as an AE.

12.6.3.3 QuantiFERON or Elispot testing

At Screening all subjects will have an IGRA test (QuantiFERON tube test or Elispot, if QuantiFERON test indicated is not available). The TB test will be repeated at completion at Week 52/WD for subjects not participating in the SFE Period. It is recommended that TB testing

be performed according to local standard medical practice during the SFE Period. Results of the tests will be reported as positive, negative, or indeterminate.

12.6.3.4 Tuberculosis questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will be completed at Screening, Baseline, and every 12 weeks thereafter including and up to Week 36 and including Week 52/WD visit.

The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question "Has the subject been in close contact with an individual with active TB, or an individual who has recently been treated for TB?" at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has LTB or active TB (see Exclusion Criterion 16, Section 6.2). A "Yes" response to any of the questions during the study should trigger further assessments to determine if the subject has either LTB or active TB infection (see Appendix 18.12).

Subjects with a LTB infection must receive prophylactic therapy prior to continuing study drug (if allowed by prophylactic therapy specific protocol).

Subjects with active TB infection must be withdrawn from the study and will have further assessments.

12.6.3.5 Tuberculosis management

For inclusion in the study, see Section 6.2 (Exclusion Criterion 16).

It is the Sponsor's requirement that all subjects who are on LTB treatment at Baseline must comply with the full therapy course (see Section 6.2, Exclusion Criterion 16).

LTB infection and active TB identified during study

During the study, subjects who develop evidence of LTB infection or active TB must immediately stop further administration of study medication and will be referred to an appropriate TB specialist (pulmonologist or infectious disease specialist) for further evaluation. Evidence of LTB infection is defined as subject's IGRA test converts to positive or indeterminate (and confirmed indeterminate on repeat), or the subject's questionnaire or history and physical indicates that TB infection or exposure may have occurred. Evidence of active TB includes, in addition to the aforementioned tests, signs and symptoms of organ involvement. In either situation, the subject should be carefully assessed by a TB specialist for active TB. Subjects diagnosed with active TB or LTB infection should receive appropriate TB or prophylaxis therapy.

If a TB specialist excludes an active TB infection the subject can proceed with the study drug no earlier than 4 weeks after the start of an appropriate prophylactic therapy.

Any presumptive diagnosis or diagnosis of a TB infection is a reportable event. Confirmed active TB must be reported as an SAE; confirmed LTB as AESI (please see Sections 12.2 and 12.3). The Investigator is to complete and submit the TB follow up form provided.

The subject should be transferred to the care of his/her physician and managed according to the best available standard of care. Subjects identified as having converted to active TB during the

study must be withdrawn and scheduled to return for the Week 52/WD visit as soon as possible but no later than the next scheduled study visit and complete all Week 52/WD visit assessments.

The subject should be encouraged to complete a FU visit (8 weeks after the Week 52/WD visit).

If infection with NTMB is identified during the study, the same procedure as for active TB acquired during the study must be followed.

Subjects with LTB infection must not undergo IGRA testing. The IGRA test should be used for any protocol mandated monitoring.

Follow-up information of suspected and confirmed TB cases should be provided to UCB at least after 3, 9, and 12 months of the start date of anti-TB treatment, including hematological and biochemical safety parameters, x-ray evolution data, and TB diagnostic procedures used to follow up and confirm recovery of TB.

12.6.4 Vital signs

Subjects should be sitting for 5 minutes prior and during the collection of blood pressure, pulse rate, and respiration rate measurements.

Vital signs, including temperature will be measured at all on-site visits including the FU visit (8 weeks after the Week 52/WD visit) with the exception of the Week 1 visit (respiration rate will be measured at Screening and Baseline only unless the subject has an AE). It is recommended that vital signs be measured according to local standard medical practice during the SFE Period.

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 Adherence to protocol

The investigator should not deviate from the protocol. However, the investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor.

After implementation of such measure, the Investigator must notify the CPM of the Sponsor within 24 hours and follow any local regulatory requirements.

13.2 Monitoring

UCB (or designee) will monitor the study to meet the Sponsor's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a CRO or a contract monitor.

The Investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review all CRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of CRFs, ensure that all protocol requirements, applicable authorities' regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

13.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies/printouts of electronic CRFs (eCRFs) are not considered acceptable source documents. Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or QoL questionnaires, for example. Source documents should be kept in a secure, limited access area.

The following data will be recorded directly in the electronic patient reported outcome (ePRO) Tablet on site and will not appear in a source document as defined above:

- Patient Reported Outcome questionnaires: SF-36, EQ-5D-3L, PGADA, BASDAI, BASFI, ASQoL, MOS Sleep Scale, Total and Nocturnal Spinal Pain Questionnaire

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the subject's source documents. The Investigator will authorize the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records such as MRI records must be saved and stored as instructed by UCB (or designee).

13.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, ECG tracings, x-ray films, laboratory notes). All data reported on the CRF should be supported by source documents, unless otherwise specified in Section 13.2.1.

13.3 Data handling

13.3.1 Case report completion

This study will be using remote data capture (RDC); the Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRF and in all required reports.

Serious adverse event reporting will be done using the SAE form (see Section 12.2) while also entering the event in the appropriate eCRF section. The safety database and the clinical database will be reconciled during the study and discrepancies will be corrected as needed.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF. Access to the RDC will be given after training has been received. A training certificate will be provided and filed.

Detailed instructions on the use of the RDC will be provided in the eCRF Completion Guidelines.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be re-approved by the Investigator. Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

13.4 Electronic reporting outcome

Compared to the paper patient questionnaires, the new electronic options have several advantages combining handheld devices in conjunction with online technologies in order to send subject self assessments directly to a central server. The collected data could then be reviewed in real time for monitoring of subject symptoms and compliance. The ePRO possibilities will be used in this study.

This study will use an electronic Site Tablet having a large screen and intuitive fingertip data entry to ensure all questionnaire data are captured appropriately, completely and on time. Only subjects' data will be collected with the tablets; the data of both the physicians (joint counts and PhGADA) and WPS will be entered directly in the eCRF or collected on worksheets.

Access to the system by site personnel will be given after training has been received. A training certificate will be provided and filed. The Investigator should maintain a list of personnel authorized to enter data into the electronic ePRO device.

13.5 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data monitoring system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Case Report form data are entered into the clinical database by site personnel.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The Investigator will keep a list containing all subjects enrolled into the study. This list remains with the Investigator and is used for unambiguous identification of each subject. The list contains the subject identification number, full name, date informed consent signed, date of screening, and the hospital number or National Health Security number, if applicable.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

13.6 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC also should be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused study drug and other material in accordance with UCB procedures for the study.

Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator, as appropriate:

- Return of all study data to the Sponsor or its representative
- Data clarification and/or resolution
- Accountability, reconciliation, and arrangements for used and unused study drugs
- Review of site study records for completeness
- Discussion/reminder on archiving responsibilities

Further details will be given in the monitoring guidelines.

13.7 Archiving and data retention

The Investigator will maintain adequate records for the study, including CRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's study master file.

13.8 Audit and inspection

The Investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing

study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform UCB (or designee).

13.9 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

14 STATISTICS

A description of statistical methods follows and will be described in more detail in the SAP.

14.1 Definition of analysis sets

The Enrolled Set (ES) will consist of all subjects who have given informed consent.

The Randomized Set (RS) will consist of all subjects randomized into the study.

The Safety Set (SS) will consist of all subjects who have received at least 1 dose of study medication.

The Full Analysis Set (FAS) will consist of all subjects in the RS who have received at least 1 dose of study medication.

The Per Protocol Set (PPS) will consist of subjects in the FAS without any important protocol deviations that may influence the validity of the primary efficacy data. The PPS may also require that a defined period of exposure to study medication be completed. Important protocol deviations will be predefined and evaluated prior to study unblinding/database lock.

The SFE Safety Set (SFE-SS) will be defined as all subjects who continued into the SFE Period and who received at least 1 dose of CZP in the SFE Period.

14.2 General statistical considerations

All efficacy analyses will be performed using the FAS. The PPS will be used for a sensitivity analysis on the primary endpoint only.

The statistical analysis of the primary efficacy variable and selected secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure. The predefined order of hypothesis testing, each at a 2-sided 0.05 significance level for the comparison between CZP 200mg Q2W and placebo, will be performed in the sequence shown below. After the first test, each subsequent test is performed only if the previous test is significant in favor of CZP at the 2-sided 0.05 level. Note that the first test relates to the primary efficacy variable while the others provide the sequence testing for selected secondary efficacy variables.

1. ASDAS-MI response at Week 52
2. ASAS40 response at Week 12
3. Change from Baseline in BASDAI at Week 12
4. Change from Baseline in BASFI at Week 12
5. ASAS40 response at Week 52
6. Change from Baseline in BASDAI at Week 52
7. Change from Baseline in BASFI at Week 52
8. Change from Baseline in SI joint SPARCC score at Week 12
9. Change from Baseline in ASQoL at Week 52
10. Change from Baseline in nocturnal spinal pain (NRS) at Week 52
11. Number of subjects with AU or new AU flares through Week 52

<u>Hierarchical testing of efficacy variables for Canada (and any other country where applicable or where requested by Regulatory Authorities):</u>

1. ASAS40 response at Week 12
2. ASDAS-MI response at Week 52
3. Change from Baseline in BASDAI at Week 12
4. Change from Baseline in BASFI at Week 12
5. ASAS40 response at Week 52
6. Change from Baseline in BASDAI at Week 52
7. Change from Baseline in BASFI at Week 52
8. Change from Baseline in SI joint SPARCC score at Week 12
9. Change from Baseline in ASQoL at Week 52
10. Change from Baseline in nocturnal spinal pain (NRS) at Week 52
11. Number of subjects with AU or new AU flares through Week 52

Variables evaluated over time will be summarized using imputed and observed case values. Further details on data summarization will be provided in the SAP.

14.3 Planned efficacy analyses

The primary efficacy variable measurement for this study is based on ASDAS-MI response at Week 52. The associated primary outcome of the study will be defined as a composite endpoint that is achieved if a subject fulfills the following 2 components:

1. Remain in the study and on the double-blind study treatment through 52 weeks
2. Achieve an ASDAS-MI response at 52 weeks

For simplicity, this primary efficacy variable will be referred to as ASDAS-MI response at Week 52. However, the composite definition as described above will apply when this endpoint is analyzed. The primary analysis for this endpoint will be based on logistic regression. The odds ratio of the ASDAS-MI responder rates at Week 52 will be estimated and tested between treatment groups using a logistic regression model with factors of treatment group, region, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+). If the logistic regression model is unable to converge, then the MRI/CRP classification variable may be dropped from the model to facilitate convergence. The study design is likely to result in some sites with a small number of enrolled subjects. The use of region as a stratification variable and as a factor in the model is intended to combine study centers in similar geographic regions. The geographic regions to be used will be defined in the IXRS and in the SAP. Given the composite endpoint definition described above, there will be no missing data for the primary endpoint, as subjects that discontinue the double-blind study treatment prior to Week 52 or who do not have an ASDAS-MI status at Week 52 are considered nonresponders to the double-blind study treatment.

As described in Section 6.3, subjects who discontinue the double-blind study treatment will not necessarily be withdrawn from the study. In an attempt to minimize missing data, efforts will be made to continue to collect safety and efficacy data on these subjects through study completion. Sensitivity analyses will be performed to evaluate the impact of missing data on the analysis of the primary efficacy variable (see Section 14.8).

For Canada (and any other country where applicable or where requested by Regulatory Authorities), the primary efficacy variable measurement is the ASAS40 response at Week 12. Analysis of the ASAS40 response at Week 12 will be performed as described above for ASDAS-MI response at Week 52. Similar to the ASADAS-MI efficacy endpoint, the ASAS40 will be treated as a composite endpoint when it is analyzed. Specifically, subjects will need to: 1) achieve the relevant response (ASAS40); and 2) remain in the study and on their randomized double-blind study treatment through Week 12.

Subgroup analyses by age, gender, race, symptom duration, smoking history, HLA-B27 genotype, anti-CZP Ab (ADAb) status, region, prior anti-TNF exposure, Baseline SPARCC score ≥5, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) will be performed for the primary efficacy variable. Subgroup analyses will be summarized using descriptive statistics only.

14.4 Secondary efficacy analyses

The changes from Baseline in BASDAI and BASFI at Week 12 and Week 52, change from Baseline in ASQoL at Week 52, and change from Baseline in nocturnal spinal pain at Week 52 are specified as secondary efficacy variables. As these are continuous variables, missing data must be handled using a different approach from what is specified for the primary efficacy

endpoint (a responder variable). In the current study, Investigators will be given discretion to discontinue the double-blind study treatment for subjects not responding in order to provide them with alternative therapy to treat the condition. Therefore, in many cases, missing efficacy data due to the double-blind study treatment discontinuation should be dependent on the observed efficacy scores, but independent of unobserved data. This would be consistent with a missing at random (MAR) assumption. However, the possibility of discontinuation due to tolerability or other unobserved data cannot be completely discounted. Therefore, a missing not at random mechanism will be used for the analysis of continuous secondary efficacy variables.

A reference-based multiple imputation (MI) procedure will be used for this analysis, which will impute missing data as well as data at the time points following the discontinuation of the double-blind study treatment for both the CZP and placebo groups. This procedure will use an imputation model developed based on available data from the placebo group, thereby assuming a placebo trajectory for missing data following study treatment discontinuation for subjects in both treatment groups (Mallinckrodt, 2013). The estimand being evaluated in this case is the difference in the outcome of improvement in all randomized subjects at the planned endpoint, attributable to the initially randomized medication. This is an effectiveness estimand of the de facto hypothesis which has been referred to as “estimand 6” (Mallinckrodt, 2012).

Additionally, change from Baseline in SI joint SPARCC score at Week 12 is a continuous secondary efficacy variable. The same MI procedure specified as the main analysis approach for BASDAI and BASFI will be used to account for missing SPARCC data. However, it should be noted that, unlike BASDAI and BASFI, SPARCC score will not be measured at any time points between Baseline and Week 12, meaning that those are the only 2 time points that can be considered in the evaluation of SPARCC score at Week 12. Comparisons between treatment groups will be made using an analysis of covariance (ANCOVA) model on the imputed data set. The model will include Baseline score, treatment group, region, and MRI/CRP classification.

The ASAS40 response at Week 12 and Week 52 are responder secondary efficacy endpoints. (For Canada and any other country where applicable or where requested by Regulatory Authorities, the ASAS40 response at Week 12 is the primary efficacy variable; the ASAS40 response at Week 52 and the ASDAS-MI response at Week 52 are secondary efficacy variables). As a responder variable, ASAS40 will be analyzed using logistic regression based on a model similar to the one described for the primary analysis.

The number of subjects with new onset post-Baseline AU or new AU flares through Week 52 is a categorical secondary efficacy endpoint for all regions. Subjects with a new event at one or more visits post-Baseline will be classified as having had a flare, subjects without new events at all visits post-Baseline will be classified as not having had a flare. As a dichotomous outcome variable, treatment groups will be compared for differences using logistic regression based on a model similar to the one described for the primary analysis.

The comparison of CZP 200mg Q2W to placebo as described above for the ASAS40 response, BASDAI, and BASFI at Week 12 and Week 52, for SI joint SPARCC score at Week 12, for ASQoL at Week 52, nocturnal pain score at Week 52, and number of subjects with AU or new AU flares through Week 52 will be part of the fixed sequence testing procedure outlined in Section 14.2.

Additionally, sensitivity analyses will be conducted on these secondary efficacy endpoints. In particular, the assumptions related to missing data will be investigated further. These analyses are described in Section 14.8.

An additional secondary efficacy variable is the number of subjects with relevant changes to background medication. This variable will be based on whether or not subjects take certain pre-specified background medications during the course of the study and will be defined in the SAP. The analysis for this variable will use the same logistic regression model described for the primary variable.

14.5 Other efficacy analyses

Double-Blind Period treatment group comparisons for CZP 200mg Q2W versus placebo will be performed based on the change from Baseline in other selected efficacy variables. These analyses will be performed using an ANCOVA model including Baseline score, treatment group, region, and MRI/CRP classification. The treatment differences and corresponding 95% confidence intervals (CIs) will be calculated based on the adjusted means. Missing values or values observed after discontinuing the double-blind study treatment will be imputed using last observation carried forward (LOCF). The following variables will be analyzed in this manner:

- PGADA
- Morning stiffness (average of BASDAI questions 5 and 6)
- BASMI
- Total spinal pain
- SF-36, PCS, MCS, and individual domains
- Fatigue NRS
- Sleep Problems Index II domains of the MOS Sleep scale

Statistical analyses will also be done for BASDAI, BASFI, and SI joint SPARCC score for time points not specified in the secondary efficacy analyses, using the same analysis methods described in Section 14.4. Additionally, ASDAS and ASAS response variables will be analyzed using a logistic regression model similar to the one specified for the primary analysis at time points not covered in the primary and secondary efficacy analyses.

These comparisons are not part of the multiplicity-controlled testing procedure described in Section 14.2. The p-values reported for these analyses will not be adjusted for multiplicity and will be considered nominal. Exploratory statistical comparisons for CZP 200mg Q2W versus placebo will also be performed for WPS scores using the nonparametric bootstrap-t method. This will be explained in greater detail in the SAP.

Summary statistics will be provided for other variables. Summary statistics will consist of frequency tables and percentages for categorical variables. Continuous variables will be summarized by visit (where applicable) with descriptive statistics (number of available observations [n], mean, median, SD, minimum and maximum). Details on the analysis of the other endpoints will be provided in the SAP.

14.6 Planned safety and other analyses

The Safety Set (SS) will be used for analysis of safety data from the Double-Blind Period as well as the combined Double-Blind and SFE Period (as applicable), and the SFE-SS will be used for analysis of safety data from the SFE Period.

14.6.1 Safety analyses

The frequency of all AEs during the study period will be presented for each treatment group separately by system organ class, high level term, and preferred term. The data will be displayed as number of subjects experiencing the AEs, percentage of subjects, and number of AEs. Data will also be corrected for exposure and reported by 100 patient-years.

Since subjects will be permitted to change background medications and because they may also discontinue the double-blind study treatment and initiate a new treatment (including biologics) during the course of the study, special consideration will be given to how AEs are attributed to the double-blind study treatment. This, along with other specialized AE summaries, will be described in greater detail in the SAP.

Laboratory evaluations and vital signs will be analyzed over time in the SS for observed cases and at the end of treatment.

14.6.2 Pharmacokinetic and immunogenicity variable analysis

Certolizumab pegol plasma concentrations will be tabulated and summarized by treatment group for each visit at which samples were taken using the geometric mean, geometric coefficient of variation, 95% CIs, arithmetic mean, arithmetic SD, minimum and maximum. Individual plasma concentrations for CZP and anti-CZP levels versus time will be produced on the same graph.

Immunogenicity will be assessed through listing of individual results by subject and summary table. Immunogenicity data will be correlated with PK and efficacy readout. In addition, immunogenicity will be correlated with possible safety findings.

14.7 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on study conduct or on the primary efficacy outcome for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented prior to unblinding to confirm exclusion from analysis sets.

14.8 Handling of dropouts or missing data

For analysis purposes, the primary efficacy variable is defined as a composite endpoint in which it is necessary to achieve ASDAS-MI at Week 52 and to remain on randomized double-blind study treatment through Week 52 in order to be considered a responder (see Section 14.3). Because this composite endpoint definition does not allow for a missing response status, no formal method for handling missing data is needed in the primary efficacy analysis. However, in order to assess the impact of various missing data assumptions on the analysis, additional sensitivity analyses of the primary efficacy variable will be performed as follows:

- Including observed data at Week 52: The observed data at Week 52 will be used and analyzed according to randomized treatment, regardless of whether or not the subject is still on his/her randomized double-blind study treatment at that time. Despite efforts to continue to collect data on all subjects (even if they discontinue the double-blind study treatment), there may still be subjects with missing data at Week 52. Such subjects will be considered as non-responders in accordance with the composite endpoint definition outlined above. The same logistic regression model specified for the primary analysis will be used.
- MI: The Markov Chain Monte Carlo (MCMC) method will be used to impute intermittent missing data. The resulting multiply imputed data sets will be monotone missing and will be imputed using monotone regression (assuming a MAR pattern). Note that the MI procedure will be done on the continuous ASDAS variable, which will be dichotomized for the logistic regression analysis. Ankylosing Spondylitis Disease Activity Score data collected following the discontinuation of double-blind study treatment will be treated as missing in the original data set for this sensitivity analysis.
- Tipping point analysis: In this analysis, various assumptions will be made about average outcomes among the subsets of subjects who prematurely discontinued double-blind study treatment. Various "delta adjustments" will be made to the assumed responses among missing data in each treatment arm with varying degrees of plausibility (O'Kelly, 2014). The goal of the tipping point analysis is to identify assumptions about the missing data under which the conclusions change, ie, under which there is no longer evidence of a treatment effect. Then, the plausibility of such assumptions would be discussed. Further details of this procedure will be described in the SAP.
- Observed case analysis: This analysis will only include the observed data for subjects still on the original double-blind study treatment. Data collected after the discontinuation of double-blind study treatment and all other missing data will be excluded from the analysis. The same logistic regression model specified for the primary efficacy analysis will be performed.

Sensitivity analyses of the primary efficacy variable for Canada (and any other country where applicable or where requested by Regulatory Authorities), ASAS40 response at Week 12, will mirror the approach described above for ASDAS-MI at Week 52.

The sensitivity analyses of the secondary binary efficacy variables (ASAS40 at Week 52) will be as follows:

- Including observed data at Week 52: As described for the primary efficacy variable.
- MI: As described for the primary efficacy variable. Note that as ASAS40 is a composite of 4 different variables, the MI procedure will be performed on each of these components, and the ASAS40 response will be derived based on the multiply imputed datasets.
- Reference-based MI: This procedure will impute missing data as well as data at the time points following the discontinuation of the double-blind study treatment for both the CZP and placebo groups. This procedure will use an imputation model developed based on data from the placebo group (Mallinckrodt, 2013). The estimand being evaluated in this case is the difference in the outcome of improvement in all randomized subjects at the planned

endpoint, attributable to the initially randomized medication, which has been referred to as "estimand 6" (Mallinckrodt, 2012).

- Observed case analysis: As described for the primary efficacy variable.

For the secondary efficacy variable "number of subjects with AU or new AU flares through Week 52," missing values should only occur in the unlikely case that a subject does not have any post-Baseline AU assessments performed. Therefore, sensitivity analyses for this variable will focus on analyses adjusting for exposure time at risk such as event rate, incidence rate, and confidence interval.

The sensitivity analyses of secondary continuous efficacy variables (the change from Baseline in BASDAI and BASFI at Weeks 12 and 52, and the change from Baseline in the SI joint SPARCC score at Week 12, change from Baseline in ASQoL at Week 52, and change from Baseline in nocturnal spine pain at Week 52) will be as follows:

- Including observed data at Week 52: As described for the primary efficacy variable.
- MI: As described for the primary efficacy variable.
- Observed case analysis: As described for the primary efficacy variable.
- LOCF

Missing data for the other efficacy variables described in Section 14.5 will be handled as follows:

- With imputation: Non-responder imputation for binary variables and LOCF for continuous variables (as described in Section 14.5)
- Observed case analysis: As described for the primary efficacy variable.

Additionally, algorithms for imputing missing or partial dates for safety evaluations will be detailed in the SAP.

14.9 Planned interim analysis and data monitoring

An interim analysis is planned after the completion of the Double-Blind Period of the last subject at Week 52. At this time, the database from the Double-Blind Period will be locked, the treatment codes will be made available to relevant UCB personnel, and an interim study report will be written. The Investigators and subjects will remain blind to the assigned CZP dose regimen of the Double-Blind Period. After the completion of the SFE Period of the last subject, the database will be locked, and a final study report will be written. From the Week 52 Visit onward, subjects will be treated with open-label CZP until the last dosing visit of the study (SFE Week 104).

Regular monitoring of safety data collected during clinical studies will be performed as described in the Safety Signal Detection in the Ongoing Clinical Trials Charter for CZP.

A specific data monitoring, steering, or evaluation committee is not planned for this study.

14.10 Determination of sample size

Subjects will be randomized in a 1:1 ratio to the CZP 200mg Q2W and placebo treatment groups. The expected responder rates for ASDAS-MI at Week 52 are 40% and 20% for CZP and

placebo, respectively. A total sample size of 300 (150 subjects per treatment group) provides 95% power to detect a statistically significant difference in the ASDAS-MI responder rate at Week 52 between CZP and placebo, using a 2-sided significance level of 0.05.

With Protocol Amendment 4, ASAS40 response at Week 12 was elevated to be the primary efficacy variable for Canada (and any other country where applicable or where requested by Regulatory Authorities); however, the study was fully enrolled at the time of this amendment. The expected responder rates for ASAS40 response at Week 12 are also 40% for CZP and 20% for placebo, which are identical to the assumed response rates cited for ASDAS-MI at Week 52. Therefore, the planned total sample size of 300 would provide 95% power for this variable, as well.

15 ETHICS AND REGULATORY REQUIREMENTS

15.1 Informed consent

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the written Informed Consent form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection. An additional Informed Consent form for participation in the substudy should be completed.

If the Informed Consent form is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

All studies conducted at centers in the USA must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent form. A CRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

15.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject. The Investigator will fill in the subject identifying information and medical emergency contact information. The Investigator will instruct the subject to keep the card with them at all times.

15.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, Informed Consent form, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

15.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at Screening.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital

admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

15.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

16 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements, as applicable.

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18 APPENDICES

18.1 ASAS classification criteria for axial SpA

ASAS classification criteria for axial SpA

(for subjects with chronic back pain ≥3 months and age at onset <45 years)

Imaging criteria	**ASAS clinical criteria for axial SpA**
Sacroiliitis (MRI or radiographs*) plus ≥1 SpA feature	HLA-B27 plus ≥2 other SpA features

SpA features**	
Inflammatory back pain***	Psoriasis
Arthritis	Crohn's disease/ulcerative colitis
Enthesitis (heel)	HLA-B27
Uveitis	Elevated CRP
Dactylitis	

CRP=C-reactive protein; MRI=magnetic resonance imaging; HLA-B27=human leukocyte antigen B27; NSAID=nonsteroidal anti-inflammatory drug; SpA=spondyloarthritis

* Active inflammatory lesions of sacroiliac joints with definite bone marrow oedema/osteitis suggestive of sacroiliitis associated with spondyloarthritis in MRI or radiographic sacroiliitis grade 2 to 4 bilaterally or grade 3 to 4 unilaterally according to modified NY criteria.

** Family history for SpA and Good response to NSAIDs are excluded as SpA feature criteria.

***Inflammatory back pain according to ASAS criteria for Axial SpA defined as the presence of 4 out of 5 of the following parameters:

1) age at onset <45 years
2) insidious onset
3) improvement with exercise
4) no improvement with rest
5) pain at night (with improvement upon getting up)

18.2 Modified NY criteria for ankylosing spondylitis

Subjects meeting the NY criteria in the context of this protocol are defined as subjects meeting the definite AS diagnosis according to the modified NY criteria below.

Modified NY criteria for ankylosing spondylitis

Diagnosis
1) Clinical criteria
a) Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest.
b) Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
c) Limitation of chest expansion relative to normal values corrected for age and sex.
2) Radiologic criterion
Sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3 to 4 unilaterally.
Grading
1) Definite ankylosing spondylitis if the radiologic criterion is associated with at least 1 clinical criterion

Note: A second grading of "probably ankylosing spondylitis" is part of the modified NY criteria, but it is not applicable for this study. It is included here for completeness. The grading will be probable ankylosing spondylitis if three clinical criteria are present and the radiologic criterion is present without any signs or symptoms satisfying the clinical criteria (other causes of sacroiliitis should be considered).

18.3 Table of corticosteroid equivalent doses

Table of corticosteroid equivalent doses

Prednisone (reference)	10mg
Cortisone	50mg
Hydrocortisone	40mg
Prednisolone	10mg
Triamcinolone	8mg
Methylprednisolone	8mg
Betamethasone	1.5mg
Dexamethasone	1.5mg

Corticosteroid equivalent doses (with reference to prednisone 10mg dose) (Meikle and Tyler, 1977)

The following information (eg, questionnaire) is copyrighted and UCB does not have permission to disclose the contents.

18.9 PGADA (NRS)

NRS patient global disease activity

How active was your spondyloarthritis on average during the last week?

Please tick the box that represents your answer (i.e. [10])

0	1	2	3	4	5	6	7	8	9	10

Not active very active

The following information (eg, questionnaire) is copyrighted and UCB does not have permission to disclose the contents.

18.11 Total spinal pain NRS and nocturnal spinal pain NRS

NRS pain
Please tick the box that represents your answer (i.e. 10)

1. Total SpinePain
How much pain of your spine due to spondyloarthritis do you have?

0	1	2	3	4	5	6	7	8	9	10

no pain — most severe pain

2. Nocturnal SpinePain
How much pain of your spine due to spondyloarthritis do you have at night?

0	1	2	3	4	5	6	7	8	9	10

no pain — most severe pain

18.12 Tuberculosis Sample Worksheet

Tuberculosis Worksheet (Source)

Evaluation for signs and symptoms of tuberculosis questionnaire

The following questions are to be asked of every subject for evaluation of risk factors for tuberculosis (TB). Responses to each question must be documented on this source document.

- Has the patient been in close contact (i.e., sharing the same household or other enclosed environment) with an individual with active TB or an individual who has recently been treated for TB? ☐ Yes ☐ No
- Does the subject have a new cough lasting more than 14 days or a change in a chronic cough? ☐ Yes ☐ No
- Does the subject have night sweats? ☐ Yes ☐ No
- Does the subject have a persistent fever? ☐ Yes ☐ No
- Does the subject have unintentional weight loss (more than 10% of body weight)? ☐ Yes ☐ No
- Is the subject [or subject's parents/legally acceptable representative(s) if subject is a minor] a hospital employee or in frequent contact with hospital employees (example: providing catering service to hospital employees or married to one)? ☐ Yes ☐ No
- Is the subject frequently exposed to other subjects (study visits/ hospitalizations) that are on study drug or other immunosuppressive drugs? ☐ Yes ☐ No
- Does the subject reside in, did the subject ever reside in, or is the subject frequently traveling to a TB endemic region(s)? ☐ Yes ☐ No
- Does the subject reside in, did the subject ever reside in, or is the subject frequently visiting densely populated areas such as highly urbanized city centers? ☐ Yes ☐ No
- Does the subject frequently use public transportation? ☐ Yes ☐ No
- Is the subject in frequent contact with elderly or underprivileged populations (homeless or other people needing social assistance)? ☐ Yes ☐ No
- Does the subject appear malnourished? ☐ Yes ☐ No
- Has the subject had an abnormal chest x-ray since the last evaluation? ☐ Yes ☐ No

(v.2009-09-09)

18.13 Protocol Amendment 1

Rationale for the amendment

The substantial amendment includes several changes to clarify and/or add supporting information regarding the procedures and assessments, and to remove inconsistencies and errors: a range of sensitivity analyses, previously discussed with the regulatory authorities, to evaluate the impact of missing data on the analysis of the primary efficacy variable.

Other changes included the following: the exclusion criterion regarding the upper limit of normal of the liver function tests for subjects who are not treated with methotrexate, the requirement for plasma samples to be analyzed to confirm the washout of specific prohibited medications was removed, and the reporting-needs of particular physician-completed assessments in the eCRFs were clarified. Two tables were included to assist the Investigators in identifying the assessments to be performed when subjects switch to alternative treatments. Inconsistencies in the laboratory assessments performed, the definition of study treatment, and the use of Week 52 and Week 52/Withdrawal (WD) visit were corrected, study personal information was updated, and minor editorial changes were made.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- The study contact information is updated
- Week 52 and Week 52/Early Withdrawal visits are updated to Week 52/WD visit throughout the protocol, as defined in the Schedule of Assessments.
- Double-blind study treatment administration during the Double-Blind Period has been defined consistently throughout the protocol.
- The laboratory assessments to be performed throughout the study are updated so that they are described consistently throughout the protocol.
- Magnetic resonance imaging (MRI) for the spine is to be performed at Week 12, along with the already planned sacroiliac (SI) MRI.
- "Are Patient-Reported Outcome Instruments for Ankylosing Spondylitis Fit-For-Purpose for the Axial Spondyloarthritis Patient? A Qualitative and Psychometric Analysis" by van Tubergen et al has been published and the protocol is updated to reflect the publication
- The protocol is updated to reflect that the recording of the Physician's Global Assessment of Disease Activity (PhGADA), joint count, and Work Productivity Survey (WPS) will be on the electronic Case Report form (eCRF) only.
- For subjects who discontinue the study treatment during Study Period 2, the assessments completed at the scheduled visit do not need to be repeated at the withdrawal treatment (wdt) Week 0 visit of the alternative schedule. Therefore, 2 additional tables are added to facilitate the Investigators understanding of which remaining assessments are required to be performed, when the subject enterseither the open-label certolizumab pegol (CZP) or the alternative treatment schedule.

- The use of the Interactive response system (IXRS) is updated to clarify that it will be used to register subjects attending Visit 1 without issuing any kit number.
- The current study does not analyze the samples collected data for methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), nonsteroidal anti-inflammatory drug (NSAID), corticosteroids, and the washout of any prohibited medications; the text that describes this is deleted.
- The Safety Set (SS) definition is updated.
- Following discussion with the regulatory authorities, a range of different sensitivity analyses have been included to investigate the missing data assumption.
- The use of graphs for individual plasma concentrations for CZP and anti-CZP levels versus time analysis is included.
- Other changes made in this amendment are to provide clarification or are administrative in nature, including minor editorial changes to abbreviations.

Specific changes

This section displays the modifications in this amendment compared with the Final Protocol dated 01 Jun 2015. The changes are displayed in the order of appearance.

Change #1

Study Contact Information

Sponsor Study Physician

Name:	[redacted], MD
Address:	[redacted]
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Sponsor Study Physician

Name:	[redacted], MD
Address:	[redacted]
Phone:	[redacted]
Fax:	[redacted]

Change #2

List of abbreviations

The following abbreviations have been added:

Apo	apolipoprotein
HbA1c	Hemoglobin A1c
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MI	multiple imputation

Change #3

List of abbreviations

The following abbreviation has been deleted:

TNFα	tumor necrosis factor alpha

Change #4

Section 1 Summary, paragraphs 3, 4, 6, 7, 12, 15, and 16

Additionally, subjects must have had an inadequate response to, have a contraindication to, or have been intolerant to at least 2 NSAIDs. Inadequate response to a NSAID is defined as lack of response to at least 14 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID. Eligible subjects will be allocated to the following study treatments in a 1:1 ratio:

- CZP administered subcutaneously (sc) at the dose of CZP 400mg at Weeks 0, 2, and 4 followed by CZP 200mg every 2 weeks (every other week; Q2W) sc (starting at Week 6)
- Placebo

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), study treatments will be administered sc at the study site by dedicated, unblinded, and adequately trained site personnel. The study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. All subjects will receive training for self-injection at the study site at Weeks 10 and 12. During the training at the Weeks 10 and 12 visits, the study treatment will be self-administered under the supervision of the dedicated unblinded study personnel.

Subjects whose disease activity cannot be controlled by study medication and changes in background therapy (including and not limited to analgesics, NSAIDs, and slow-acting antirheumatic drug [SAARDs]) will be permitted to withdraw from the double-blind study drug. Subjects will either transition to open-label treatment offered by UCB with the marketed product of CZP, after Week 52, ie, completion of all study assessments, or at the discretion of the Investigator and in accordance with the local regulatory requirements for a maximum duration of 2 years or until marketing authorization is granted for CZP (if applicable), whichever comes first, or subjects will transition to receive other treatment (including biologics). These subjects will remain in the study until the assessment of the primary endpoint at Week 52.

All subjects, including those withdrawn from study treatment, will have a FU Visit 8 weeks after their final Week 52 visit.

The primary efficacy variable is Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) response at Week 52. The secondary efficacy variables are Assessment in Axial SpondyloArthritis International Society 40% (ASAS40) response at Weeks 12 and 52, change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Weeks 12 and 52, change from Baseline in BASDAI at Weeks 12 and 52, change from Baseline in Sacroiliac-Spondyloarthritis Research Consortium of Canada (SI-SPARCC) score at Week 12, and the number of subjects without relevant changes to background medication.

Safety variables to be assessed are adverse events (AEs), vital signs, physical examination, and measurements of laboratory parameters. In addition, subjects will be evaluated at Screening, Baseline, and at every 12 weeks thereafter up to and including Week 36 for signs and symptoms of latent or active tuberculosis (TB) infection and risk factors for exposure to TB using the TB questionnaire.

Approximately 900 subjects will be screened in order to have 300 subjects (150 subjects per treatment group) randomized into the study. Randomization will be stratified by presence of sacroiliitis on MRI and elevated CRP to ensure balanced treatment allocation across three subgroups: MRI+/CRP+; MRI+/CRP-; MRI-/CRP+. For each subject, the study will last a maximum of 66 weeks and will consist of 3 periods:

- Screening Period lasting up to 6 weeks
- Double-Blind, placebo-controlled Period for 52 weeks
- FU Period 8 weeks after the Week 52/Withdrawal (WD) visit.

Have been changed to:

Additionally, subjects must have had an inadequate response to, have a contraindication to, or have been intolerant to at least 2 NSAIDs. Inadequate response to a NSAID is defined as lack of

response to at least 14 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID. Eligible subjects will be allocated to the following double-blind study treatments in a 1:1 ratio:

- CZP administered subcutaneously (sc) at the dose of CZP 400mg at Weeks 0, 2, and 4 followed by CZP 200mg every 2 weeks (every other week; Q2W) sc (starting at Week 6)
- Placebo

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site by dedicated, unblinded, and adequately trained site personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. All subjects will receive training for self injection at the study site at Weeks 10 and 12. During the training at the Weeks 10 and 12 visits, the double-blind study treatment will be self administered under the supervision of the dedicated unblinded study personnel.

Subjects whose disease activity cannot be controlled by study medication and changes in background therapy (including and not limited to analgesics, NSAIDs, and slow-acting antirheumatic drugs [SAARDs]) will be permitted to withdraw from the double-blind study drug. Subjects will either transition to open-label CZP treatment offered by UCB or to other treatment (including biologics) at the discretion of the Investigator until the assessment of the primary endpoint at Week 52. At the completion of the Week 52 visit, and in accordance with the local regulatory requirements, CZP will be provided for a maximum duration of 2 years or until marketing authorization is granted for CZP (if applicable), whichever comes first.

All subjects, including those withdrawn from double-blind study treatment, will have a FU visit 8 weeks after their final Week 52 visit.

The primary efficacy variable is Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) response at Week 52. The secondary efficacy variables are Assessment in Axial SpondyloArthritis International Society 40% (ASAS40) response at Weeks 12 and 52, change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Weeks 12 and 52, change from Baseline in BASDAI at Weeks 12 and 52, change from Baseline in SI-Spondyloarthritis Research Consortium of Canada (SPARCC) score at Week 12, and the number of subjects without relevant changes to background medication.

Safety variables to be assessed are adverse events (AEs), vital signs, physical examination, and measurements of laboratory parameters. In addition, subjects will be evaluated at Screening, Baseline, and at every 12 weeks thereafter up to and including Week 52/Withdrawal (WD) for signs and symptoms of latent or active tuberculosis (TB) infection and risk factors for exposure to TB using the TB questionnaire.

Approximately 900 subjects will be screened in order to have 300 subjects (150 subjects per treatment group) randomized into the study. Randomization will be stratified by presence of sacroiliitis on MRI and elevated CRP to ensure balanced treatment allocation across 3 subgroups: MRI+/CRP+; MRI+/CRP-; MRI-/CRP+. For each subject, the study will last a maximum of 66 weeks and will consist of 3 periods:

- Screening Period lasting up to 6 weeks

- Double-Blind, Placebo-Controlled Period for 52 weeks
- FU Period 8 weeks after the Week 52/Withdrawal (WD) visit.

Change #5

Section 2.2 Burden of disease in axSpA, paragraph 2

Several large observational and noninterventional cohort studies (Cuirea et al, 2013; Sieper and van der Heijde, 2013a) reported a similar burden of disease at study baseline across AS studies (captured through BASFI and BASDAI) in nonradiographic as well as radiographic axSpA (captured through BASDAI). A literature review of clinical studies in both populations (Callhoff et al, 2015) and (RAPID-AxSpA) (Landewe et al, 2014) confirmed this finding in the clinical study setting.

Has been changed to:

Several large observational and noninterventional cohort studies (Cuirea et al, 2013; Sieper and van der Heijde, 2013a) reported a similar burden of disease at study baseline across AS studies (captured through BASFI and BASDAI) in nonradiographic as well as radiographic axSpA (captured through BASDAI). A literature review of studies in both populations (Callhoff et al, 2015) and a recent study with CZP (RAPID-AxSpA) (Landewe et al, 2014) confirmed this finding in the clinical study setting.

Change #6

Section 2.4 Current management of axial spondyloarthritis, paragraphs 3 and 4

Patients who are intolerant of or have inadequately responded to NSAIDs, or those in whom NSAIDs are contraindicated, have limited treatment options. Tumor necrosis factor alpha (TNFα) inhibitors (CZP, adalimumab [ADA] etanercept [ETN] infliximab [IFX]), golimumab [GOL]) are currently the only effective and approved treatment options as of Dec 2014; IFX and GOL are indicated for active AS only, while CZP, ADA, and ETN are indicated for axSpA without radiographic evidence of AS (nr-axSpA) as an addition to the AS indication in several regions.

At the 2014 Annual Meeting of the ACR/SPARTAN group a draft treatment guideline was presented for the subject suffering from both AS and nr-axSpA. These guidelines recommend the use of a TNF inhibitor after NSAID treatment.

Have been changed to:

Patients who are intolerant of or have inadequately responded to NSAIDs, or those in whom NSAIDs are contraindicated, have limited treatment options. Tumor necrosis factor-alpha inhibitors (TNFi) (CZP, adalimumab [ADA] etanercept [ETN] infliximab [IFX]), golimumab [GOL]) are the only effective and approved treatment options as of Dec 2014; IFX and GOL are indicated for active AS only, while CZP, ADA, and ETN are indicated for axSpA without radiographic evidence of AS (nr-axSpA) as an addition to the AS indication in several regions.

At the 2014 Annual Meeting of the ACR/SPARTAN group a draft treatment guideline was presented for the subject suffering from both AS and nr-axSpA. These guidelines recommend the use of a TNFi after NSAID treatment.

Change #7

Section 2.5 Rationale, paragraph 2

To address the unmet need for treatment options for nr-axSpA, AS0006 will be conducted focusing on subjects who do not meet the mNY classification criteria for AS (see Appendix 18.2). Data suggest that patients with objective signs of inflammation and high disease activity are likely to run a chronic disease course and unlikely to be well managed on conventional therapy (Rudwaleit ACR 2013). Furthermore, studies where anti-TNFs have been withdrawn in nr axSpA patients show that patients flare quickly and hence the disease is unlikely to go into spontaneous remission. However, there are no long-term prospective studies to assess how patients meeting the ASAS classification criteria respond to conventional therapies. With the conduct of this 52-week study comparing CZP to placebo in combination with standard of care, a better understanding should be gained of how a long-term anti-TNF therapy compares to standard of care in patients meeting the ASAS criteria with objective signs of inflammation. Moreover, patients whose disease cannot be managed under the blinded study treatment conditions will be able to discontinue the study treatment and transition to either open-label CZP or other therapies.

Has been changed to:

To address the unmet need for treatment options for nr-axSpA, AS0006 will be conducted focusing on subjects who do not meet the mNY classification criteria for AS (see Appendix 18.2). Data suggest that patients with objective signs of inflammation and high disease activity are likely to run a chronic disease course and unlikely to be well managed on conventional therapy (Rudwaleit ACR 2013). Furthermore, studies where anti-TNFs have been withdrawn in nr-axSpA patients show that patients flare quickly and hence the disease is unlikely to go into spontaneous remission. However, there are no long-term prospective studies to assess how patients meeting the ASAS classification criteria respond to conventional therapies. With the conduct of this 52-week study comparing CZP to placebo in combination with standard of care, a better understanding should be gained of how a long-term anti-TNF therapy compares to standard of care in patients meeting the ASAS criteria with objective signs of inflammation. Moreover, patients whose disease cannot be managed under the blinded study treatment conditions will be able to discontinue the double-blind study treatment and transition to either open-label CZP or other therapies.

Change #8

Section 4.1.3 Other efficacy variables

The following bullet has been added:

- Change from Baseline in sacroiliitis grading to Week 52 for structural damage

Change #9

Section 4.2.3 Pharmacogenomic variables

For individuals consenting to the genomics substudy, blood samples will be drawn for possible genetic/epigenetic, genomic, proteomic, and metabolomics analysis at Baseline and Week 12. Additional samples will be collected for genomics, proteomics, and metabolomics analysis only, at Baseline, Weeks 4, 12, and 52. Collection of the samples will enable the exploratory evaluation of biomarkers relative to disease activity, drug treatment, and inflammatory and immune response processes. The nature and format of these tentative analyses will be determined when the results of the main study are made available. The samples will be stored at -80°C at the central biorepository for up to 20 years.

Has been changed to:

For individuals consenting to the genomics substudy, blood samples will be drawn for possible genetic/epigenetic, genomic, proteomic, and metabolomics analysis at Baseline and Week 12. Additional samples will be collected for genomics, proteomics, and metabolomics analysis only, at Weeks 4 and Week 52/WD. Collection of the samples will enable the exploratory evaluation of biomarkers relative to disease activity, drug treatment, and inflammatory and immune response processes. The nature and format of these tentative analyses will be determined when the results of the main study are made available. The samples will be stored at -80°C at the central biorepository for up to 20 years.

Change #10

Section 4.3 Immunological variables, paragraph 1

4.3 Immunological variable(s)

Anti-CZP antibody (anti-CZP Ab) concentrations will be assessed at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52, and the FU Visit (8 weeks after the Week 52/WD Visit). In addition, the anti CZP Ab concentrations will be assessed in subjects who withdraw from study drug and transition to open-label CZP. The number and percent of subjects with anti-CZP Ab concentrations above 2.4 units/mL will be reported as follows:

Has been changed to:

4.3 Immunological variables

Anti-CZP antibody (anti-CZP Ab) concentrations will be assessed at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52/WD, and the FU visit (8 weeks after the Week 52/WD visit). In addition, the anti-CZP Ab concentrations will be assessed in subjects who withdraw from study drug and transition to open-label CZP. The number and percent of subjects with anti-CZP Ab concentrations above 2.4 units/mL will be reported as follows:

Change #11

Section 4.4 Safety variables, paragraphs 4 through 6

Clinical laboratory values (hematology, biochemistry, urinalysis) will be collected and assessed at Screening, Baseline, Weeks 2, 4, 8, 12, 24, 36, at the end of study Completion at Week 52/Early Withdrawal Visit and at the FU Visit (8 weeks after the Week 52/WD Visit). In addition, clinical laboratory values will be collected and assessed at study visits during the administration of open-label CZP in subjects who withdraw from the study treatment.

Furthermore, CRP will be collected and assessed either in a blinded or open manner at Screening, 3 to 5 days before Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and at the end of study Completion at Week 52/Early Withdrawal Visit and at the FU Visit (8 weeks after the Week 52/WD Visit).

At Screening, all subjects will have an Interferon-Gamma Release Assay (IGRA) test (QuantiFERON® TB test or Elispot® test, when the QuantiFERON test indicated is not available), and a chest x-ray read (or, if done, computed tomography of the chest) which must be reported consistent with standard clinical reporting practice by an experienced qualified TB specialist, radiologist, or a pulmonologist, who is specifically required to look for signs of active TB or signs of past/inactive TB infection. The official report of the imaging must specifically indicate the absence of findings suggestive of current active TB or prior inactive TB. In addition to a physical examination done intermittently throughout the study, subjects will be evaluated at Screening, Baseline, and every 12 weeks thereafter up to and including Week 36, including the Completion/Early Withdrawal Visit, for signs and symptoms of latent or active TB infection and risk factors for exposure to TB using the TB questionnaire

Have been changed to:

Clinical laboratory values (hematology, biochemistry, urinalysis) will be collected and assessed at Screening, Baseline, Weeks 2, 4, 8, 12, 24, 36, at the end of study completion at Week 52/WD Visit and at the FU Visit (8 weeks after the Week 52/WD Visit). In addition, clinical laboratory values will be collected and assessed at study visits during the administration of open-label CZP in subjects who withdraw from the double-blind study treatment.

Furthermore, CRP will be collected and assessed either in a blinded or open manner at Screening, 3 to 5 days before Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and at the end of study completion at Week 52/WD visit and at the FU visit (8 weeks after the Week 52/WD visit).

At Screening, all subjects will have an Interferon-Gamma Release Assay (IGRA) test (QuantiFERON® TB test or Elispot® test, when the QuantiFERON test indicated is not available), and a chest x-ray read (or, if done, computed tomography of the chest) which must be reported consistent with standard clinical reporting practice by an experienced qualified TB specialist, radiologist, or a pulmonologist, who is specifically required to look for signs of active TB or signs of past/inactive TB infection. The official report of the imaging must specifically indicate the absence of findings suggestive of current active TB or prior inactive TB. In addition to a physical examination done intermittently throughout the study, subjects will be evaluated at Screening, Baseline, and every 12 weeks thereafter up to and including the Week 52/WD visit,

for signs and symptoms of latent tuberculosis (LTB) or active TB infection and risk factors for exposure to TB using the TB questionnaire.

Change #12

Section 5.1.1 Study periods

The study includes 3 periods. An injection schedule is provided in Section 7.2.2.

Period 1 (Screening Period): 1 to 6 weeks before Baseline:

Prior to any study activities, subjects will be asked to read and sign the Informed Consent form for the conduct of the study. A separate informed consent form will also be obtained from subjects consenting to the use of their blood samples in a substudy for possible genetic, genomic/epigenetic, and proteomic analysis.

Laboratory data is to be obtained to verify the doses of MTX, SSZ, hydroxychloroquine (HCQ), NSAIDs, and corticosteroids, if used, are stable. Laboratory data will also be collected to ensure the washout of any medications not permitted for use during the study has been performed, and to initiate latent TB treatment where necessary. Concomitant medications permitted during the study should remain stable for at least 4 weeks prior to Baseline.

Sacroiliac-joint x-ray (not older than 12 months before Baseline and verified by central reading during the Screening Period) must prove that the subject belongs to the mNY-negative axSpA subpopulation, ie, does not have sacroiliitis grade ≥2 bilaterally or grade 3 to 4 unilaterally. Potentially eligible axSpA subjects without suitable SI-joint x-ray must undergo the x-ray with central reading within the Screening Period. SI-joint x-rays (read centrally) will allow discrimination of subjects with AS and without definitive evidence for sacroiliitis on x-ray (mNY negative-axSpA). Subjects with AS (mNY-positive) must be excluded from further participation in this study.

Confirmed mNY-negative axSpA subjects must undergo an MRI later during the Screening Period for central reading with results from the central reading available by no later than at the Baseline visit.

Additionally the subjects must get a further measurement of CRP 3 to 5 days before Baseline (Week 0).

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

Eligible subjects will be allocated to the following study treatments in a 1:1 ratio:

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

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), study treatments will be administered sc at the study site by dedicated, unblinded and adequately trained site personnel. The study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. All subjects will receive training for self-injection at the study site on Weeks 10 and 12. During the training on Weeks 10 and 12 visits, the study treatment will be

self-administered under the supervision of the unblinded study personnel. Concomitant medications permitted during the study should remain stable for at least 4 weeks prior to the Week 12, 24, and 52 assessments.

Period 3 (Follow-Up Period):

All subjects, including those withdrawn from study treatment, will have a FU Visit 8 weeks after the Week 52/WD visit.

Alternative schedules

Subjects who discontinue the study treatment and enter open-label treatment with CZP or other treatments (including biologics) will follow alternative schedules of assessments. Assessments are to be continued as at Week 12 every 12 weeks until as close as possible to Week 52 (within ±4 weeks of the originally planned Week 52 Visit) of the regular visit schedule. Subjects will then be invited to the final assessment visit at Week 52.

Has been changed to:

The study includes 3 periods. An injection schedule is provided in Section 7.2.2.

Period 1 (Screening Period): 1 day to 6 weeks before Baseline:

Prior to any study activities, subjects will be asked to read and sign the Informed Consent form for the conduct of the study. A separate informed consent form will also be obtained from subjects consenting to the use of their blood samples in a substudy for possible genetic/epigenetic, genomic, proteomic, and metabolite analysis.

Laboratory data (hematology, urine, and biochemistry tests) will be obtained, and treatment of LTB will be initiated when necessary. Subjects must undergo a TB test and complete a TB questionnaire. Bath Ankylosing Spondylitis Disease Activity Index, BASMI, and spinal mobility assessments will be performed. Concomitant medications permitted during the study should remain stable for at least 4 weeks prior to Baseline at Week 0.

Sacroiliac-joint x-ray (not older than 12 months before Baseline and verified by central reading during the Screening Period) must prove that the subject belongs to the mNY-negative axSpA subpopulation, ie, does not have sacroiliitis grade ≥2 bilaterally or grade 3 to 4 unilaterally. Potentially eligible axSpA subjects without suitable SI-joint x-ray must undergo the x-ray with central reading within the Screening Period. Sacroiliac-joint x-rays (read centrally) will allow discrimination of subjects with AS and without definitive evidence for sacroiliitis on x-ray (mNY negative-axSpA). Subjects with AS (mNY-positive) must be excluded from further participation in this study.

Confirmed mNY-negative axSpA subjects must undergo an MRI later during the Screening Period for central reading with results from the central reading available by no later than at the Baseline visit.

Additionally the subjects must get a further measurement of CRP 3 to 5 days before Baseline (Week 0).

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

Eligible subjects will be allocated to the following double-blind study treatments in a 1:1 ratio:

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

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site by dedicated, unblinded and adequately trained site personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. All subjects will receive training for self-injection at the study site on Weeks 10 and 12. During the training on Weeks 10 and 12 visits, the double-blind study treatment will be self-administered under the supervision of the unblinded study personnel. Concomitant medications permitted during the study should remain stable for at least 4 weeks prior to the Weeks 12, 24, and 52/WD assessments.

Period 3 (Follow-Up Period):

All subjects, including those withdrawn from the double-blind study treatment, will have a FU visit 8 weeks after the Week 52/WD visit.

Alternative schedules

Subjects who discontinue the double-blind study treatment and enter open-label treatment with CZP will be assessed 2 and 4 weeks after open-label CZP treatment has been initiated and every 12 weeks thereafter. Alternatively, subjects who discontinue the double-blind study treatment and receive other treatment (including biologics) will be assessed every 12 weeks after initiation of the other treatment. The alternative schedules for open-label CZP and other treatment can be found in Table 5–2 and Table 5–3, respectively. In either alternative schedule, assessments should be conducted until as close as possible to Week 52 (within ±4 weeks), where Week 52 is relative to the original randomization at Week 0. Subjects will then be invited to the final assessment visit at Week 52.

Change #13

Section 5.1.2 Study duration, paragraph 2

The estimated recruitment period is up to 15 months. The first subject first visit is planned in Quarter 3 of 2015. A completed subject is one who completes the Week 52 Visit. UCB will offer continuation of open-label treatment with the marketed product of CZP, after Week 52, ie, completion of all study assessments, on discretion of the Investigator and in accordance with the local regulatory requirements, for a maximum duration of 2 years or until marketing authorization is granted for CZP (if applicable), whichever comes first.

Has been changed to:

The estimated recruitment period is up to 15 months. The first subject first visit is planned in Quarter 3 of 2015. A completed subject is one who completes the Week 52/WD visit. Subjects will either transition to open-label CZP treatment offered by UCB or to other treatment (including biologics) at the discretion of the Investigator until the assessment of the primary endpoint at Week 52/WD. At the completion of the Week 52/WD visit, and in accordance with the local regulatory requirements, CZP will be provided for a maximum duration of 2 years or until marketing authorization is granted for CZP (if applicable), whichever comes first.

Change #14

Section 5.2 Schedule of study assessments, paragraph 3

At any time during the study course, but preferably not before Week 12, the Investigator may discontinue the study treatment and start open-label treatment with either CZP (which will be provided free of charge by UCB) or an alternative drug (eg, other treatment [including biologics]). Table 5–2 shows the schedule of assessments for subjects receiving open-label treatment with CZP and Table 5–3 shows the schedule of assessments for subjects receiving an alternative treatment (not CZP).

Has been changed to:

At any time during the study course, but preferably not before Week 12, the Investigator may discontinue the double-blind study treatment and start open-label treatment with either CZP (which will be provided free of charge by UCB) or an alternative drug (eg, other treatment [including biologics]). Table 5–2 shows the schedule of assessments for subjects receiving open-label treatment with CZP and Table 5–3 for subjects receiving an alternative treatment (not CZP).

Change #15

Section 5.2 Schedule of study assessments, Table 5–1

The following row has been added:

Table 5–1: Schedule of study assessment - Study Periods 1 to 3 (Screening until FU)

Visit #	**Scr**	**Scr day -5 to -3**	**1/ BL**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 H**	**10**	**11 H**	**12**	**13 H**	**14**	**15 H**	**16**	**17 H**	**18**	**19 H**	**20**	**21 H**	**22**	**23 H**	**24**	**25 H**	**26**	**27**	**28**	**29**
Week Protocol Activity	**-6 weeks to -1 day**		**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14 / H**	**16**	**18 / H**	**20**	**22 / H**	**24**	**26 /H**	**28**	**30 /H**	**32**	**34 / H**	**36**	**38 / H**	**40**	**42 / H**	**44**	**46 / H**	**48**	**50**	**52 / WD**	**FU[b]**
HBsAg/ antibodies to hepatitis C/HIV/HLA-B 27/CKD-EPI	X[f]																														

Change #16

Section 5.2 Schedule of study assessments, Table 5–1 (The row describing IXRS)

Table 5–1: Schedule of study assessment - Study Periods 1 to 3 (Screening until FU)

Visit #	**Scr**	**Scr day -5 to-3**	**1/ BL**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 H**	**10**	**11 H**	**12**	**13 H**	**14**	**15 H**	**16**	**17 H**	**18**	**19 H**	**20**	**21 H**	**22**	**23 H**	**24**	**25 H**	**26**	**27**	**28**	**29**
Week Protocol Activity	**-6 to -1**		**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14 / H**	**16**	**18 / H**	**20**	**22 / H**	**24**	**26 /H**	**28**	**30 /H**	**32**	**34 / H**	**36**	**38 / H**	**40**	**42 / H**	**44**	**46 / H**	**48**	**50**	**52 / WD**	**FU[b]**
IXRS	X		X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X	X	X	X

Has been changed to:

Table 5–1: Schedule of study assessment - Study Periods 1 to 3 (Screening until FU)

Visit #	Scr	Scr day -5 to -3	1/BL	2	3	4	5	6	7	8	9H	10	11H	12	13H	14	15H	16	17H	18	19H	20	21H	22	23H	24	25H	26	27	28	29
Week Protocol Activity	**-6 weeks to -1 day**		**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14/H**	**16**	**18/H**	**20**	**22/H**	**24**	**26/H**	**28**	**30/H**	**32**	**34/H**	**36**	**38/H**	**40**	**42/H**	**44**	**46/H**	**48**	**50**	**52/WD**	**FU[b]**
IXRS	X		X		X	X	X	X	X	X		X		X		X		X		X		X		X		X		X	X	X	X

Change #17

Section 5.1 Schedule of study assessments, Table 5-1: footnotes d to o have been reordered and footnotes with changes are noted.

[a] Informed consent: Prior to any study activities, subjects will be asked to read and sign the informed consent form for the conduct of the study. A separate informed consent form will also be obtained from subjects consenting to the use of their blood samples in a substudy for possible genetic, genomic/epigenetic, and proteomic analysis.

[d] Testing to rule out hepatitis B surface antigen and antibodies to hepatitis C and testing for HLA-B27 and abnormalities for estimated Glomerular Filtration Rate as measured by CKD-EPI are to be performed at Screening only.

[f] Pregnancy testing must be carried out for women of childbearing potential and will be serum testing at the Screening Visit and FU and urine testing (dipstick) at Baseline and Week 52/Withdrawal.

[g] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Weight is to be measured at Screening, Week 24, and at Completion at Week 52/Early Withdrawal. Height will be measured at the Baseline Visit only.

[k] Magnetic resonance imaging of the spine and SI joints to be performed at Screening, Weeks 12 (SI only), 52, or Early Withdrawal Visit if MRI was performed more than 12 weeks prior to Early Withdrawal Visit.

[n] At on-site visit days (Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), study treatments will be administered sc at the study site by dedicated, unblinded and adequately trained site personnel. The study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. From Week 52 onwards, after completion of all on site assessments and procedures, the subject may receive further open-label treatment with CZP to be supplied to discontinued subjects or another biologics at the discretion of the Investigator.

[o] All subjects will receive training for self-injection at the study site on Weeks 10 and 12. During the training at the Weeks 10 and 12 visits, the study treatment will be self-administered under the supervision of the unblinded study personnel.

Have been changed to:

[a] Informed consent: Prior to any study activities, subjects will be asked to read and sign the informed consent form for the conduct of the study. A separate informed consent form will also be obtained from subjects consenting to the use of their blood samples in a substudy for possible genetic/epigenetic, genomic, proteomic, and metabolite analysis.

[d] Subjects will be encouraged to be in fasting condition at Baseline and at Week 52/WD or at the time the subject shifts to alternative treatment, for Apo A1, ApoB, and lipoprotein(a) assessments.

[e] HbA1c will be measured at Baseline and Week 52/WD.

[f] Testing to rule out HBsAg, antibodies to hepatitis C, and HIV will be performed. In addition, testing for HLA-B27 and abnormalities for estimated glomerular filtration rate as measured by CKD-EPI are to be performed.

[h] Pregnancy testing must be carried out for women of childbearing potential: A serum test will be performed at the Screening visit and FU, and urine testing (dipstick) at Baseline and Week 52/WD.

[i] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Weight is to be measured at Screening, Week 24, and at completion at Week 52/WD. Height will be measured at the Baseline visit only.

[m] Magnetic resonance imaging of the spine and SI joints to be performed at Screening and at the Week 12 and at the Week 52/WD visits if MRI was performed more than 12 weeks prior to WD visit.

[p] Contact IXRS to register the visit and obtain next kit number, where applicable.

[q] At on-site visit days (Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site by dedicated, unblinded and adequately trained site personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. From Week 52 onwards, after completion of all onsite assessments and procedures, the subject may receive open-label CZP at the discretion of the Investigator.

[r] All subjects will receive training for self-injection at the study site on Weeks 10 and 12. During the training at the Weeks 10 and 12 visits, the double-blind study treatment will be self-administered under the supervision of the unblinded study personnel.

Change #18

Section 5.2 Schedule of study assessments

The following row has been added:

Table 5–2: Schedule of alternative study assessment with CZP - after subject discontinuation of study treatment

Visit #	wdt	2 wdt	3 wdt				5 wdt						6 wdt			
Week Protocol Activity	**0**	**2**	**4**	**6H**	**8H**	**10**	**12**	**14 H**	**16H**	**18 H**	**20 H**	**22 H**	**24 and Q12W**		**52/ WD**	**FU[a]**
Telephone contact[k]					X				X		X					

Change #19

Section 5.2 Schedule of study assessments

Table 5–2: Schedule of alternative study assessment with CZP - after subject discontinuation of study treatment

Visit #	1 wdt	2 wdt	3 wdt				5 wdt						6 wdt			
Week Protocol Activity	**0**	**2**	**4**	**6 H**	**8 H**	**10**	**12**	**14 H**	**16H**	**18 H**	**20 H**	**22 H**	**24 and Q12W**		**52/WD**	**FU[a]**

Has been changed to:

Table 5–2: Schedule of alternative study assessment with CZP - after subject discontinuation of the double-blind study treatment

Visit #	1 wdt	2 wdt	3 wdt				4 wdt						5 wdt			
Week Protocol Activity	0	2	4	6H	8H	10H	12	14H	16H	18H	20H	22H	24 and Q12W		52/WD	FU[a]

Change #20

Section 5.2 Schedule of study assessments, Table 5–2

Table 5–2: Schedule of alternative study assessment with CZP - after subject discontinuation of study treatment

Visit #	**1 wdt**	**2 wdt**	**3 wdt**				**5 wdt**						**6 wdt**			
Week Protocol Activity	**0**	**2**	**4**	**6 H**	**8 H**	**10**	**12**	**14 H**	**16H**	**18 H**	**20 H**	**22 H**	**24 and Q12W**		**52/WD**	**FU[a]**
CZP administration sc	X[i]	X[i]	X[i]	X	X	X	X	X	X	X	X	X	X	**Continue assessments as at W24 every 12 weeks until as close as possible to W52 of the original visit schedule. Subject will then be invited to the final assessment visit at W52**	X	X

Has been changed to:

Table 5–2: Schedule of alternative study assessment with CZP - after subject discontinuation of the double-blind study treatment

Visit #	**1 wdt**	**2 wdt**	**3 wdt**				**4 wdt**						**5 wdt**			
Week Protocol Activity	**0**	**2**	**4**	**6H**	**8H**	**10H**	**12**	**14H**	**16H**	**18H**	**20H**	**22H**	**24 and Q12W**		**52/WD**	**FU[a]**
CZP administration sc	X[l]	X[l]	X[l]	X	X	X	X	X	X	X	X	X	X[m]	**Continue assessments as at W24 every 12 weeks until as close as possible to W52 of the original visit schedule. Subject will then be invited to the final assessment visit at W52**		

Change #21

Section 5.2 Schedule of study assessments, Table 5–2: footnotes have been reordered and footnotes with changes are noted.

Note: All weeks are ±3 days compared to Baseline. Week 0 of the alternative schedule starts 2 weeks after the last dose of the study treatment.

[d] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Weight is to be measured at wdt Week 0, Week 24, and at completion at Week 52/Early Withdrawal Visit.

[e] If the last Q12W assessment for a subject who discontinues study treatment is ≤4 weeks before the final assessments visit at Week 52, the assessment should be cancelled and the subject should instead be invited to undergo the final assessments visit at Week 52 (the Week 52 Visit is to be scheduled 52 weeks (±3 days) after Baseline).

Have been changed to:

Note: All weeks are ±3 days compared to Baseline. Week 0 of the alternative schedule starts 2 weeks after the last dose of the double-blind study treatment.

[c] Subjects will be encouraged to be in fasting condition at the time the subject shifts to alternative treatment, for Apo A1, ApoB, and lipoprotein(a) assessments.

[d] HbA1c will be measured at wdt Week 0 and Week 52/WD.

[f] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Weight is to be measured at wdt Week 0, Week 24, and at completion at Week 52/WD.

[g] If the last Q12W assessment for a subject who discontinues study treatment is ≤4 weeks before the final assessments visit at Week 52/WD, the assessment should be cancelled and the subject should instead be invited to undergo the final assessments visit at Week 52 (the Week 52/WD visit is to be scheduled 52 weeks [±3 days] after Baseline).

[k] A telephone contact will be made with the subject every 4 weeks after the on-site visit (ie, at Weeks 8H, 16H, 22H, and every 4 weeks after Week 24 until Week 52/WD visit).

[m] CZP administration will be continued Q2W.

Change #22

Section 5.2 Schedule of study assessments, Table 5-3: table title

Table 5–3: Schedule of alternative study assessment with other treatment (including biologics) - after subject discontinuation of the study treatment

Has been changed to:

Table 5–3: Schedule of alternative study assessment with other treatment (including biologics) - after subject discontinuation of the double-blind study treatment

Change #23

Additional text has been added for other treatment administration for Week 12, Week 24, and Q12W

Table 5–3: Schedule of alternative study assessment with other treatment (including biologics) - after subject discontinuation of the double-blind study treatment

Visit #	1 wdt	2 wdt	3 wdt			
Week **Protocol Activity**	**0**	**12**	**24 and Q12W**	**Continue assessments as at W24 every 12 weeks until as close as possible to W52 of the original visit schedule. Subject will then be invited to the final assessment visit at W52 ±4 weeks.**	**52/WD**	**FU[a]**
Other treatment administration		Follow the regimen of the particular alternative treatment.				

Has been changed to:

Table 5–3: Schedule of alternative study assessment with other treatment (including biologics) - after subject discontinuation of the double-blind study treatment

Visit #	1 wdt	2 wdt	3 wdt			
Week **Protocol Activity**	**0**	**12**	**24 and Q12W**	**Continue assessments as at W24 every 12 weeks until as close as possible to W52 of the original visit schedule. Subject will then be invited to the final assessment visit at W52 ±4 weeks.**	**52/WD**	**FU[a]**
Other treatment administration		Follow the regimen of the particular alternative treatment. Telephone contact to be performed on the discretion of the investigator				

Change #24

Section 5.2 Schedule of study assessments, Table 5-3: footnotes have been reordered and changes to footnotes are noted.

Note: All weeks are ±3 days compared to Baseline. Week 0 of the alternative schedule starts 2 weeks after the last dose of the study treatment.

[b] If the last Q12W assessment for a subject who discontinues study treatment is ≤4 weeks before the final assessments visit at Week 52 the assessment should be cancelled and the subject should instead be invited to undergo the final assessments visit at Week 52/WD (the Week 52 visit is to be scheduled 52 weeks [±3 days] after Baseline).

Have been changed to:

Note: All weeks are ±3 days compared to Baseline. Week 0 of the alternative schedule starts 2 weeks after the last dose of the double-blind study treatment.

[b] Subjects will be encouraged to be in fasting condition at the time the subject shifts to alternative treatment, for Apo A1, ApoB, and lipoprotein(a) assessments.

[c] HbA1c will be measured at wdt Week 0.

[d] If the last Q12W assessment for a subject who discontinues study treatment is ≤4 weeks before the final assessments visit at Week 52/WD, the assessment should be cancelled and the subject should instead be invited to undergo the final assessments visit at Week 52/WD (the Week 52/WD visit is to be scheduled 52 weeks [±3 days] after Baseline).

Change #25

Section 5.2 Schedule of study assessments

The following paragraphs have been added:

At any time during the study course, but preferably not before Week 12, the Investigator may discontinue the double-blind study treatment and start open-label treatment with either CZP (which will be provided free of charge by UCB) or an alternative drug (eg, other treatment [including biologics]).

The determination by the Investigator to switch a subject from double-blind study treatment to either open-label CZP or other treatment will generally be done after the subject has completed the assessments at a given scheduled study visit. That study visit then becomes the wdt Week 0 visit of the given alternative schedule of assessments. Since many of the assessments required at the wdt Week 0 visit may have already been completed as part of the originally scheduled study visit, only those not already done at that visit should be completed. Table 5–4 outlines which additional study assessments would be required at wdt Week 0 for subjects switching to the open-label CZP alternative schedule, and Table 5–5 shows this information for subjects switching to the other treatment alternative schedule.

It may be possible that an Investigator determines that a subject should switch to the alternative schedule with either open-label CZP or another treatment without initiating the alternative treatment at the study visit when this determination is made. In this case, the subject will come

back another day shortly thereafter to initiate the treatment and to complete all assessments outlined on the relevant alternative schedule of assessments (see Table 5–4 or Table 5–5) for the wdt Week 0 visit. It is important then to schedule the wdt Week 0 and the subsequent on-site visits accordingly in order to end up at Week 52 with the same visit date as originally planned for the regular double-blind study course.

Change #26

Section 5.2 Schedule of study assessments

The following tables have been added:

Table 5–4: Schedule of study assessments – additional assessments for wdt 0 visit required for subjects transitioning to open-label CZP

Visit #[a]	1/ BL	2	3	4	5	6	7	8	9 H	10	11 H	12	13 H	14	15 H	16	17 H	18	19 H	20	21 H	22	23 H	24	25 H	26	27
Week **Protocol Activity**	0	1	2	4	6	8	10	12	14 /H	16	18 /H	20	22 /H	24	26 /H	28	30 /H	32	34 /H	36	38 /H	40	42 /H	44	46 /H	48	50
Vital signs									X		X		X		X		X		X		X		X		X		
Hematology/urine/ biochemistry					X		X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
CRP					X		X		X		X		X		X		X		X		X		X		X		X
Pregnancy testing					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PE					X		X		X		X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
TB questionnaire					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
BASMI & spinal mobility					X		X		X		X		X		X		X		X		X		X		X		X
BASDAI					X		X		X		X		X		X		X		X		X		X		X		X
BASFI					X		X		X		X		X		X		X		X		X		X		X		X
SF-36					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		X
ASQoL					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		X
MOS Sleep Scale					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		X
EQ-5D					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		X
MASES					X		X		X		X	X	X		X	X	X		X	X	X		X	X	X		X
Total and nocturnal spinal pain					X		X		X		X		X		X		X		X		X		X		X		X

Table 5–4: Schedule of study assessments – additional assessments for wdt 0 visit required for subjects transitioning to open-label CZP

Visit #[a]	1/ BL	2	3	4	5	6	7	8	9 H	10	11 H	12	13 H	14	15 H	16	17 H	18	19 H	20	21 H	22	23 H	24	25 H	26	27
Week **Protocol Activity**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14 /H**	**16**	**18 /H**	**20**	**22 /H**	**24**	**26 /H**	**28**	**30 /H**	**32**	**34 /H**	**36**	**38 /H**	**40**	**42 /H**	**44**	**46 /H**	**48**	**50**
Swollen and tender joint counts					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
PhGADA					X		X		X		X		X		X		X		X		X		X		X		X
PGADA					X		X		X		X		X		X		X		X		X		X		X		X
CZP plasma concentration/anti-CZP Abs/Biomarker					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
IXRS									X		X		X		X		X		X		X		X		X		
Study drug administration sc																											

BASMI=Bath Ankylosing Spondylitis Metrology Index; CRP=C reactive protein; CZP=certolizumab pegol; EQ‑5D=EuroQoL Health Status Questionnaire (5 dimensions); H=home; IXRS=Interactive Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MOS=Medical Outcomes Study; PE=physical exam; PhGADA=Physician's Global Assessment of Disease Activity; PGADA=Patient's Global Assessment of Disease Activity; sc=subcutaneously; SF‑36=Short‑Form 36‑item Health Survey; TB=tuberculosis

Table 5–5: Schedule of study assessments – additional assessments for wdt 0 visit required for subjects transitioning to alternative treatment

Visit #[a]	1/ BL	2	3	4	5	6	7	8	9 H	10	11 H	12	13 H	14	15 H	16	17 H	18	19 H	20	21 H	22	23 H	24	25 H	26	27
Week Protocol Activity	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14 /H**	**16**	**18 /H**	**20**	**22 /H**	**24**	**26 /H**	**28**	**30 /H**	**32**	**34 /H**	**36**	**38 /H**	**40**	**42 /H**	**44**	**46 /H**	**48**	**50**
Hematology/urine/ biochemistry					X		X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
CRP					X		X		X		X		X		X		X		X		X		X		X		X
PE					X		X		X		X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
BASDAI					X		X		X		X		X		X		X		X		X		X		X		X
BASFI					X		X		X		X		X		X		X		X		X		X		X		X
Total and nocturnal spinal pain					X		X		X		X		X		X		X		X		X		X		X		X
PhGADA					X		X		X		X		X		X		X		X		X		X		X		X
PGADA					X		X		X		X		X		X		X		X		X		X		X		X
CZP plasma concentration/ anti-CZP Abs/ Biomarker					X	X	X		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X
IXRS									X		X		X		X		X		X		X		X		X		

BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; CRP=C reactive protein; CZP=certolizumab pegol; H=home; IXRS=Interactive Response System; MOS=Medical Outcomes Study; PE=physical exam; PhGADA=Physician's Global Assessment of Disease Activity; PGADA=Patient's Global Assessment of Disease Activity; sc=subcutaneously

[a] Additional assessments to be performed correspond to the assessments to be performed at wdt Week 0.

Change #27

Section 5.3 Schematic diagram, Figure 5-1

CZP 400mg loading dose has been added to the figure.

Change #28

Section 5.3 Schematic diagram, Figure 5-2

"Double-blind" and "other treatment" have been added to clarify the study treatment.

Change #29

Section 6.2 Exlcusion criteria, exclusion criterion 29, first subcriterion

29. Subjects with significant laboratory abnormalities, including but not limited to:

- liver function tests >2.0xULN, if the subject is not treated with MTX and >ULN if subject is on concomitant MTX treatment

Has been changed to:

29. Subjects with significant laboratory abnormalities, including but not limited to:

- liver function tests >2.0xULN

Change #30

Section 6.3 Withdrawal criteria, paragraphs 1 and 3

If a subject is withdrawn from study treatment, the Investigator should encourage the subject to continue participation in the study in accordance with the appropriate alternative schedule of study assessments (Table 5–2 or Table 5–3). The treatment that the subject receives following withdrawal of study medication is at the discretion of the Investigator. Open label CZP for treatment to be supplied to discontinued subjects will be made available as a treatment option according to the local requirement mandated in the region. UCB will provide this medication free of charge. Alternatively, the Investigator may treat the subject with other treatments (including biologics) as deemed appropriate by local regulations. If the Investigator choses to withdraw subjects on the other therapy, the local guidelines on initiation and monitoring of the particular treatment should be followed.

Although the subject may be withdrawn from the double-blind study treatment at any time, every effort should be made to retain the subject in the study and encourage compliance of the subject with the scheduled study visits. For subjects who fail to return to study visit(s) or are considered lost to follow up, the Investigator should specifically communicate (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents). In case the attempts to direct contact the subject fail, the Investigator is encouraged to gain information about the wellbeing of the subject at the end of the regular visit schedule (Week 52) from other sources in compliance with local regulations. All results of observations and communication with the subject, including and

not limited to the relevant information on his/her wellbeing, must be recorded in the source documents.

Have been changed to:

If a subject is withdrawn from the double-blind study treatment, the Investigator should encourage the subject to continue participation in the study in accordance with the appropriate alternative schedule of study assessments (Table 5–2 or Table 5–3). The treatment that the subject receives following withdrawal of study medication is at the discretion of the Investigator, with open-label CZP available as a treatment option according to the local requirement mandated in the region. UCB will provide this medication free of charge. Alternatively, the Investigator may treat the subject with other treatments (including biologics) as deemed appropriate by local regulations. If the Investigator chooses to withdraw subjects on the other therapy, the local guidelines on initiation and monitoring of the particular treatment should be followed.

Although the subject may be withdrawn from the double-blind study treatment at any time, every effort should be made to retain the subject in the study and encourage compliance of the subject with the scheduled study visits. For subjects who fail to return to study visit(s) or are considered lost to follow up, the Investigator should specifically communicate (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents). In case the attempts to direct contact the subject fail, the Investigator is encouraged to gain information about the wellbeing of the subject at the end of the regular visit schedule (Week 52/WD) from other sources in compliance with local regulations. All results of observations and communication with the subject, including and not limited to the relevant information on his/her wellbeing, must be recorded in the source documents.

Change #31

Section 7.1 Description of investigational medicinal product(s), paragraph 1

The IMP will be supplied under the responsibility of the UCB Clinical Supply Unit. The frequency at which IMP will be supplied to each individual center will be adapted to the recruitment capacity of that center and to the expiry date of the IMP and will be managed by the interactive response system (IXRS).

Has been changed to:

The IMP (double-blind study treatment: CZP or placebo), will be supplied under the responsibility of the UCB Clinical Supply Unit. The frequency at which IMP will be supplied to each individual center will be adapted to the recruitment capacity of that center and to the expiry date of the IMP and will be managed by the interactive response system (IXRS).

Change #32

Section 7.2.1 Treatment administration, paragraph 2

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), study treatments will be administered sc at the study site by dedicated, unblinded and adequately trained site personnel. The study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. All subjects will receive training for self-injection at the study site on Weeks 10 and 12. During the training on Weeks 10 and 12 visits, the study treatment will be self administered under the supervision of the unblinded study personnel.

Has been changed to:

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site by dedicated, unblinded, and adequately trained site personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. All subjects will receive training for self injection at the study site on Weeks 10 and 12. During the training on Weeks 10 and 12 visits, the double-blind study treatment will be self-administered under the supervision of the unblinded study personnel.

Change #33

Section 7.8 Concomitant medication(s)/treatment(s)

Table 7–1: Concomitant Medications (prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
SAARDs[b]: SSZ and/or HCQ and/or MTX and/or LFN and/or AZA	Maximum allowed: SSZ ≤3g daily HCQ ≤400mg daily MTX ≤25mg weekly AZA ≤150mg/day LFN ≤20mg/day (see exclusion criteria for washout requirements)	SAARD initiated and or any change in the dose regimen in the 28 days prior to the Baseline Visit. Use of LFN in the 6 months prior to the Baseline Visit unless a cholestyramine washout has been performed. In case of a cholestyramine washout, use 28 days prior to the Baseline Visit is acceptable.	Changes in SAARD doses should not be made between Week 0 and Week 12 or within 4 weeks prior to Week 24 or Week 52 visit. SAARD dose reduction to manage intolerance or safety issues is allowed at any time during the study at the Investigator's discretion.
SAARDs: AZA, cyclosporine, cyclophosphamide, mycophenolic acid, apremilast	Up to maximum approved dose	Use within 28 days prior to the Baseline Visit	Changes in SAARD doses or initiation of a new SAARD should be avoided between Week 0 and Week 12 or within 4 weeks prior to Week 24 or Week 52

Table 7–1: Concomitant Medications (prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
			visit
Anti-TNF therapies IFX ADA ETN GOL CZP	Any dose	For IFX, ADA, and GOL, any use within the 3 months prior to the Baseline Visit. For CZP any exposure history. For ETN, use within the 28 days prior to the Baseline Visit. Only 1 previous biologic is allowed.	If biologic therapy is required the subject must be discontinued from study medication and should conduct the remaining visits according to Figure 5–2.

Has been changed to:

Table 7–1: Concomitant Medications (prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
SAARDs[b]: SSZ and/or HCQ and/or MTX and/or LFN and/or AZA	Maximum allowed: SSZ ≤3g daily HCQ ≤400mg daily MTX ≤25mg weekly AZA ≤150mg/day LFN ≤20mg/day	SAARD initiated and or any change in the dose regimen in the 28 days prior to the Baseline visit.	Changes in SAARD doses should not be made between Week 0 and Week 12 or within 4 weeks prior to Week 24 or Week 52 visit. SAARD dose reduction to manage intolerance or safety issues is allowed at any time during the study at the Investigator's discretion.
SAARDs: cyclosporine, cyclophosphamide, mycophenolic acid, apremilast	Up to maximum approved dose	Use within 28 days prior to the Baseline visit	Changes in SAARD doses or initiation of a new SAARD should be avoided between Week 0 and Week 12 or within 4 weeks prior to Week 24 or Week 52 visit
Anti-TNF therapies IFX ADA ETN GOL CZP	Any dose	Only 1 previous biologic is allowed. For IFX, ADA, and GOL, any use within the 3 months prior to the Baseline visit. For ETN, use within the 28 days prior to the Baseline visit. For CZP any exposure history.	If biologic therapy is required the subject must be discontinued from study medication and should conduct the remaining visits according to Figure 5–2.

Change #34

Section 7.9.1 Maintenance of study treatment blind, paragraph 3

If the Investigator decides to discontinue the study treatment and initiate open-label treatment with CZP or other treatment (including biologics), efforts will be made to ensure that the blinding of the previously assigned study treatment will be maintained. This is to ensure that in case open-label treatment with CZP is chosen by the Investigator, the 3 loading doses of CZP 400mg Q2W will be administered by dedicated study personnel without disclosing to the subject the use of the PFS. After the last loading dose the subject can self administer CZP until Week 52 of the regular visit schedule.

Has been changed to:

If the Investigator decides to discontinue the double-blind study treatment and initiate open-label treatment with CZP or other treatment (including biologics), efforts will be made to ensure that the blinding of the previously assigned double-blind study treatment will be maintained. Therefore, if the open-label treatment with CZP is chosen by the Investigator, the 3 loading doses of CZP 400mg Q2W will be administered by dedicated study personnel without disclosing to the subject the use of the PFS. After the last loading dose the subject can self administer CZP until Week 52/WD of the regular visit schedule.

Change #35

Section 7.10.1 Interactive Response System, paragraph 3

The IXRS will allocate kits of study medication at Week 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50.

Has been changed to:

The IXRS will allocate kits of study medication at Weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50.

Change #36

Section 8.1 Screening visit (Week -6 to Day -1): bullet point item 1 and paragraph 5

- Confirm inclusion/exclusion criteria

One rescreening of subjects with latent TB who are able to complete a minimum of 4 weeks of TB therapy within the Screening Period is permitted. In this event, all Screening assessments must be repeated.

Has been changed to:

- Confirm inclusion/exclusion criteria (to be performed within Weeks -6 and Day -1 and confirmed between Days -5 and -3 before Baseline)

One rescreen is permitted for subjects with LTB. In this event, all Screening assessments must be repeated. Subjects are allowed to start the IMP after at least 4 weeks of prophylactic TB treatment (if compliant with the local regulations on initiation of biologic therapy in subjects

with LTB) within the Screening Period. The subject is required to complete the full prophylactic treatment.

Change #37

Section 8.2 Baseline visit (Week 0), bullet point item 3

- Blood samples will be collected for hematology and biochemistry analyses

Has been changed to:

- Blood samples (subjects should be encouraged to be under fasting conditions, the same condition [fasting or not fasting] should be applied at Week 52) will be collected for hematology and biochemistry analyses (biochemistry assessment will include the measurement of apolipoprotein (Apo) A1, ApoB, lipoprotein(a), and glycated hemoglobin [HbA1c])

Change #38

Section 8.3 Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, and 50 (all visits ±3 days relative to Baseline), bulleted items 5, 8, and 28.

- Physical examination (Weeks 2, 4, 8, 12, 16, 24, and 36), including weight at Week 24 and at completion at Week 52/WD
- MRI (SI joints only, Week 12 only)
- Contact IXRS to obtain next kit number (Week 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50)

Have been changed to:

- Physical examination (Weeks 2, 4, 8, 12, 16, 24, and 36), including weight at Week 24
- MRI (spine and SI joints, Week 12 only)
- Contact IXRS to register the visit and obtain next kit number, where applicable (Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50)

Change #39

Section 8.5 Week 52/WD (±3 days)

8.5 Completion Visit (Week 52)/Early Withdrawal (±3 days)

Has been changed to:

8.5 Week 52/WD (±3 days)

Change #40

Section 8.5 Completion Visit (Week 52)/Early Withdrawal (±3 days), paragraph 1, bulleted items 2 and 10

Assessments at this visit include:

- Blood samples will be collected for hematology, biochemistry, and CRP
- MRI for spine and SI joints (at Week 52 Visit if previous MRI was performed more than 12 weeks prior to Week 52 visit)

Have been changed to:

A subject is regarded to have completed the study if s/he completes the Week 52/WD. Assessments at this visit include:

- Blood samples (subjects should be encouraged to be under fasting conditions the same condition [fasting or not fasting] at Baseline should be applied at Week 52) will be collected for hematology, biochemistry, and CRP (biochemistry assessment will include the measurement of apolipoprotein (Apo) A1, ApoB, lipoprotein(a), and HbA1c)
- MRI for spine and SI joints (at Week 52/WD visit if previous MRI was performed more than 12 weeks prior to Week 52/WD visit)

Change #41

Section 8.6 FU visit (8 weeks after the Week 52/WD visit)

8.6 FU Visit (8 weeks after the Week 52/WD visit)

Has been changed to:

8.6 FU visit (8 weeks after the Week 52/WD visit [±3 days])

Change #42

Section 8.8 Alternative visit schedules after subject discontinuation of study treatment and bullet points 2, 15 and 16. New bullet points have been added for telephone contact.

8.8 Alternative Visit schedules after subject discontinuation of study treatment

Alternative schedules for assessment for subjects who discontinue the study treatment are described in this section. Assessments are to be continued as at Week 24 every 12 weeks until as close as possible to Week 52 (within ±3 days of the originally planned Week 52 visit) of the original visit schedule. Subject will then be invited to the final assessment visit at Week 52.

The following assessments will be performed for subjects who are treated with open-label CZP after discontinuation of study treatment:

- Blood samples will be collected for hematology, biochemistry analyses, urine will be collected for urinalysis at wdt Weeks 0, 12, 24 (and Q12W), 52 and FU and CRP at Week 0, 12, 24 (and Q12W), 52, and FU (8 weeks after Week 52 Visit)

- CZP administration at wdt Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 (and Q12W), 52, and FU. Loading dose of CZP 400mg at Weeks 0, 2 and 4 must be administered by dedicated site-staff

The following assessments will be applied for subjects who receive an alternative study assessment with other treatment (including biologics) after discontinuation of study treatment:

- Blood samples will be collected for hematology, biochemistry, and urine will be collected for urinalysis at wdt Week 0, CRP analyses will be performed at wdt Weeks 0, 12, 52, and FU

Has been changed to:

8.8 Alternative visit schedules after subject discontinuation of the double-blind study treatment

The following assessments will be performed for subjects who are treated with open-label CZP after discontinuation of the double-blind study treatment:

- Blood samples will be collected for hematology, biochemistry, and CRP analyses, and urine will be collected for urinalysis at wdt Weeks 0, 12, 24 (and Q12W), 52 and FU (8 weeks after Week 52 visit)

  Note: Fasting blood samples will be collected for hematology, biochemistry, and CRP analyses at wdt Week 0 (biochemistry assessment will include the measurement of apolipoprotein (Apo) A1, ApoB, lipoprotein(a), and HbA1c). At Week 52, the biochemistry assessment will include the measurement of HbA1c.

- CZP administration at wdt Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and every 2 weeks thereafter, until Week 52. Loading dose of CZP 400mg at Weeks 0, 2, and 4 must be administered by dedicated site-staff

- Telephone contact will occur every 4 weeks after the on-site visit at the discretion of the Investigator

The following assessments will be applied for subjects who receive an alternative study assessment with other treatment (including biologics) after discontinuation of the double-blind study treatment:

- Blood samples will be collected for hematology and biochemistry analyses, and urine will be collected for urinalysis at wdt Week 0. C-reactive protein analyses will be performed at wdt Weeks 0, 12, 52, and FU

  Note: Biochemistry assessment will include the measurement of HbA1c at wdt Week 0

- Telephone contact will occur every 4 weeks after the on-site visit at the discretion of the Investigator

Change #43

Section 9.1.2 ASAS20, 40, ASAS 5/6 response, and ASAS partial remission, bulleted item 2

- Pain assessment (the average of total and nocturnal spinal pain NRS scores)

Has been changed to:

- Pain assessment (the total spinal pain NRS score)

Change #44

Section 9.1.3 ASAS-NSAID score, bulleted item 10

- Days per week: Number of days per week when the NSAID is taken. This is collected in the categories described in the days with intake category listed above. Each category corresponds to a score as follows (score in parentheses):
  - Every day (7)
  - ≥5 days/week (6)
  - 3 to 5 days/week (4)
  - 1 to 3 days/week (2)
  - <1 day/week (0.5)
  - No NSAID intake (0)

Has been changed to:

- Days per week: Proportion of days per week when the NSAID is taken. This is collected in the categories described in the days with intake category listed above. Each category corresponds to a score as follows (score in parentheses):
  - Every day (7/7)
  - ≥5 days/week (6/7)
  - 3 to 5 days/week (4/7)
  - 1 to 3 days/week (2/7)
  - <1 day/week (0.5/7)
  - No NSAID intake (0)

Change #45

Section 9.1.4 ASQoL, addition of Table 5-2 to paragraph 2

Change #46

Section 9.1.5 BASDAI, paragraph 5

The BASDAI assessments per visit are described in the schedule of study assessments Table 5-1.

Has been changed to:

The BASDAI assessments per visit are described in the schedule of study assessments Table 5-1, Table 5–2, and Table 5–3.

Change #47

Section 9.1.6 BASFI, paragraph 2

The BASFI assessments per visit are described in Table 5–1.

Has been changed to:

The BASFI assessments per visit are described in Table 5–1, Table 5–2, and Table 5–3.

Change #48

Section 9.1.7 BASMI, paragraph 2

The BASMI assessments per visit are described in Table 5–1.

Has been changed to:

The BASMI assessments per visit are described in Table 5–1 and Table 5–2.

Change #49

Section 9.1.8 Enthesitis (MASES), paragraph 2

Enthesitis assessments per visit are described in Table 5–1.

Has been changed to:

Enthesitis assessments per visit are described in Table 5–1 and Table 5–2.

Change #50

Section 9.1.9 Extra-articular assessments

The evolution of associated nonmusculoskeletal features including inflammatory bowel disease, psoriasis and uveitis (including their severity) and flare rate will be assessed as described Table 5–1.

Has been changed to:

The evolution of associated nonmusculoskeletal features including inflammatory bowel disease, psoriasis and uveitis (including their severity) and flare rate will be assessed as described Table 5–1 and Table 5–2.

Change #51

Section 9.1.10 Health status (EQ-5D), paragraph 2

This instrument is to be completed by the subject as described in Table 5–1.

Has been changed to:

This instrument is to be completed by the subject as described in Table 5–1 and Table 5–2.

Change #52

Section 9.1.11 MOS Sleep Scale, paragraph 2

Subjects will be asked to complete the MOS Sleep Scale as described in Table 5–1.

Has been changed to:

Subjects will be asked to complete the MOS Sleep Scale as described in Table 5–1 and Table 5-2.

Change #53

Section 9.1.12 MRI assessments

Magnetic Resonance Imaging according to the ASAS/Omeract definition is the presence of bone marrow oedema (BMO) or osteitis highly suggestive of SpA that is located in the typical anatomical areas (subchodral or periarticular bone marrow). There must be either more than 1 BMO lesion on 1 slice or a lesion that is present on at least two consecutive slices (Rudwaleit et al, 2009d). In practice this is very similar to the SPARCC SIJ ≥2 definition of MRI that requires at least 2 BMO lesions to be present. A recent paper showed that the sensitivity and specificity of the ASAS/Omeract and SPARCC SIJ score ≥2 definitions of MRI positive were identical (sensitivity 0.80, specificity 0.76) (Weber et al, 2014). The Berlin modification of the ASspiMRI-a is a scoring system with a concentration on short-tau-inversion recovery (STIR) sequences without other fat saturation techniques (Braun and Baraliakos, 2011, Lukas et al, 2007; Braun and van der Heijde, and 2002; Braun et al, 2003). This scoring method quantifies changes in 23 vertebral units (VU) of the spine (from C2 to S1). A VU is defined as the region between 2 virtual lines through the middle of each vertebra. Active inflammation is scored by grading the degree of BMO from 0 to 3 in 1 dimension on 1 or more consecutive slices that represent the highest level of inflammation in a particular VU. Total spine ASspiMRI-a score in the Berlin modification can range from 0 to 69. In addition to the method mentioned above, MRIs may be evaluated using other reading criteria.

Magnetic resonance imaging of the spine and SI joints will be performed at Screening, Week 12 (SI only), 52, or Withdrawal Visit if MRI was performed more than 12 weeks prior to Early Withdrawal. MRIs will be assessed centrally and scoring will be done by 2 independent readers, who are blinded to both the order of the scans and to the treatment group, using a previously reported scoring system.

Has been changed to:

Magnetic Resonance Imaging according to the ASAS/Omeract definition is the presence of bone marrow oedema (BMO) or osteitis highly suggestive of SpA that is located in the typical anatomical areas (subchondral or periarticular bone marrow). There must be either more than 1 BMO lesion on 1 slice or a lesion that is present on at least 2 consecutive slices (Rudwaleit et al, 2009d). In practice this is very similar to the SPARCC SIJ ≥2 definition of MRI that requires at least 2 BMO lesions to be present. A recent paper showed that the sensitivity and specificity of the ASAS/Omeract and SPARCC SIJ score ≥2 definitions of MRI positive were identical (sensitivity 0.80, specificity 0.76) (Weber et al, 2014). The Berlin modification of the ASspiMRI-a is a scoring system with a concentration on short-tau-inversion recovery (STIR) sequences without other fat saturation techniques (Braun and Baraliakos, 2011; Lukas et al, 2007; Braun and van der Heijde, 2002; Braun et al, 2003). This scoring method quantifies changes in 23 vertebral units (VU) of the spine (from C2 to S1). A VU is defined as the region between 2 virtual lines through the middle of each vertebra. Active inflammation is scored by grading the degree of BMO from 0 to 3 in 1 dimension on 1 or more consecutive slices that represent the highest level of inflammation in a particular VU. Total spine ASspiMRI-a score in the Berlin modification can range from 0 to 69. In addition to the method mentioned above, MRIs may be evaluated using other reading criteria.

Magnetic resonance imaging of the spine and SI joints will be performed at Screening and at the Week 12 and at the Week 52/WD visits if MRI was performed more than 12 weeks prior to Week 52/WD. Magnetic resonance images will be assessed centrally and scoring will be done by 2 independent readers, who are blinded to both the order of the scans and to the treatment group, using a previously reported scoring system.

Change #54

Section 9.1.13 PGADA (NRS), paragraph 2

The PGADA assessments per visit are described in Table 5–1.

Has been changed to:

The PGADA assessments per visit are described in Table 5–1, Table 5–2, and Table 5–3.

Change #55

Section 9.1.14 PhGADA, paragraph 3

The PhGADA will be completed as described in Table 5–1.

Has been changed to:

The PhGADA will be completed as described in Table 5–1, Table 5–2, and Table 5–3.

Change #56

Section 9.1.17 SF-36, paragraph 3

The SF-36 has been used and has shown to be responsive in axSpA (Haibel et al, 2008) and also validating in van Tubergen et al. (Manuscript validating the response has been submitted to Rheumatology). The SF-36 will be administered per visit as described in Table 5–1.

Has been changed to:

The SF-36 has been used and has shown to be responsive in axSpA (Haibel et al, 2008) and is also validated (van Tubergen et al, 2015). The SF-36 will be administered per visit as described in Table 5–1 and Table 5-2.

Change #57

Section 9.1.18 Spinal mobility, paragraph 2

Spinal mobility will be assessed as described in Table 5–1.

Has been changed to:

Spinal mobility will be assessed as described in Table 5–1 and Table 5–2.

Change #58

Section 9.1.19 Swollen and tender joint counts (44 joints evaluation), paragraph 1

The following 44 joints are to be examined for swelling and tenderness by the Principal Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. Preferably the same assessor should evaluate the subject at each arthritis assessment. The individual with this delegated duty must be listed on Form 1572.

Has been changed to:

The following 44 joints are to be examined for swelling and tenderness by the Principal Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. Preferably the same assessor should evaluate the subject at each arthritis assessment.

Change #59

Section 9.1.19 Swollen and tender joint counts (44 joints evaluation), paragraph 6

The assessments per visit are described in Table 5–1.

Has been changed to:

The assessments per visit are described in Table 5–1 and Table 5–2.

Change #60

Section 9.1.20 Total and nocturnal spinal pain NRS, paragraph 2

The pain NRS assessments per visit are described in Table 5–1.

Has been changed to:

The pain NRS assessments per visit are described in Table 5–1, Table 5–2, and Table 5–3.

Change #61

Section 12.5 Laboratory measurements, Table 12–1

Apoliproproteins and lipoprotein(a) have been added to Table12-1 and a repeat of "others" has been removed from the "others" column

Change #62

Section 12.6.1 Pregnancy testing

Pregnancy testing must be carried out for women of childbearing potential and will consist of serum testing at Screening and FU and urine testing (dipstick) at Baseline and Week 52/Withdrawal FU.

Has been changed to:

Pregnancy testing must be carried out for women of childbearing potential and will consist of serum testing at Screening and FU and urine testing (dipstick) at Baseline, at wdt Week 0 of the alternative study assessment (for subjects administering either open-label CZP or alternative treatment), and at Week 52/WD.

Change #63

Section 12.6.3 Assessment and management of TB and TB risk factors, paragraph 13

Subjects who prematurely discontinue treatment for latent TB, or, in the opinion of the Investigator or Sponsor, are noncompliant with anti-TB therapy must discontinue further use of study medication and be immediately withdrawn. Once withdrawn from study treatment, subjects should return for the Study Completion/Withdrawal Visit, complete all Early Withdrawal assessments, and complete a FU Visit (8 weeks after the Week 52/WD-visit).

Has been changed to:

Subjects who prematurely discontinue treatment for LTB, or, in the opinion of the Investigator or Sponsor, are noncompliant with anti-TB therapy must discontinue further use of study medication and be immediately withdrawn. Once withdrawn from study treatment, subjects should return for the Week 52/WD visit, complete all Week 52/WD assessments, and complete a FU visit (8 weeks after the Week 52/WD visit).

Change #64

Section 12.6.3.2 Chest x-ray, paragraph 1

A plain posteroanterior chest x-ray (or, if done, computed axial tomography of the chest) must be done within 3 months prior to the Screening Visit. The chest x-ray must be clear of signs of TB infection (previous or current) before first study drug administration. The chest x-ray will be repeated at Completion Week 52/Withdrawal Visit (if chest x-ray was performed more than 12 weeks prior to Early Withdrawal Visit), only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

Has been changed to:

A plain posteroanterior chest x-ray (or, if done, computed axial tomography of the chest) must be done within 3 months prior to the Screening visit. The chest x-ray must be clear of signs of TB infection (previous or current) before first study drug administration. The chest x-ray will be repeated at Week 52/WD visit (if chest x-ray was performed more than 12 weeks prior to Week 52/WD visit), only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

Change #65

Section 12.6.3.4 Tuberculosis questionnaire, paragraph 1

The questionnaire “Evaluation of signs and symptoms of tuberculosis” should be used as a source document. The questionnaire will be completed at Screening, Baseline, and every 12 weeks thereafter including and up to Week 36 and at Completion at Week 52/Early Withdrawal Visit. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers “Yes” to the question “Has the subject been in close contact with an individual with active TB, or an individual who has recently been treated for TB?” at Screening is excluded. A “Yes” response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has latent or active TB (see Exclusion Criterion 16, Section 6.2). A “Yes” response to any of the questions during the study should trigger further assessments to determine if the subject has either latent TB or active TB infection (see Appendix 18.12).

Has been changed to:

The questionnaire “Evaluation of signs and symptoms of tuberculosis” should be used as a source document. The questionnaire will be completed at Screening, Baseline, and every 12 weeks thereafter including and up to Week 36 and including Week 52/WD visit. The

questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question "Has the subject been in close contact with an individual with active TB, or an individual who has recently been treated for TB?" at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has LTB or active TB (see Exclusion Criterion 16, Section 6.2). A "Yes" response to any of the questions during the study should trigger further assessments to determine if the subject has either LTB or active TB infection (see Appendix 18.12).

Change #66

Section 12.6.3.5 Tuberculosis management, paragraph 6

The subject should be transferred to the care of his/her physician and managed according to the best available standard of care. Subjects identified as having converted to active TB during the study must be withdrawn and scheduled to return for the Withdrawal Visit as soon as possible but no later than the next scheduled study visit and complete all Early Withdrawal Visit assessments.

Has been changed to:

The subject should be transferred to the care of his/her physician and managed according to the best available standard of care. Subjects identified as having converted to active TB during the study must be withdrawn and scheduled to return for the Week 52/WD visit as soon as possible but no later than the next scheduled study visit and complete all Week 52/WD visit assessments.

Change #67

Section 13.2.1 Definition of source data, paragraph 2 and bulleted items 1 and 2

The following data will be recorded directly in the PC Tablet on site and will not appear in a source document as defined above:

- Patient outcome questionnaires: SF-36, EQ-5D-3L, OMERACT flare questionnaire, PGADA, WPS-RA and the socio-professional status
- Investigator's assessments: PhGADA and the swollen and tender joint counts

Have been changed to:

The following data will be recorded directly in the electronic patient reported outcome (ePRO) Tablet on site and will not appear in a source document as defined above:

- Patient Reported Outcome questionnaires: SF-36, EQ-5D-3L, PGADA, BASDAI, BASFI, ASQoL, MOS Sleep Scale, Total and Nocturnal Spinal Pain Questionnaire

Change #68

Section 13.3.1 Case report completion, paragraph 2

The following paragraph has been deleted:

The study will also use an electronic device (Site Tablet) to capture the PhGADA and joint counts (see Section 13.4).

Change #69

Section 13.4 Electronic reporting outcome, paragraph 2

This study will use an electronic Site Tablet having a large screen and intuitive fingertip data entry to ensure all questionnaire data are captured appropriately, completely and on time. Not only subjects' data will be collected with the tablets, physicians' data (joint counts and PhGADA) will be entered directly.

Has been changed to:

This study will use an electronic Site Tablet having a large screen and intuitive fingertip data entry to ensure all questionnaire data are captured appropriately, completely and on time. Only subjects' data will be collected with the tablets; the data of both the physicians (joint counts and PhGADA) and WPS will be entered directly in the eCRF or collected on worksheets.

Change #70

Section 13.5.1 Subject Screening and Enrollment log/Subject Identification Code list

Heading 13.5.1 has been deleted.

Change #71

Section 14.1 Definition of analysis sets, paragraph 3

The Safety Set (SS) will consist of all subjects in the RS who have received at least 1 dose of study medication.

Has been changed to:

The Safety Set (SS) will consist of all subjects who have received at least 1 dose of study medication.

Change #72

Section 14.2 General statistical considerations, paragraph 2

The statistical analysis of the primary efficacy variable and selected secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure. The predefined order of hypothesis testing, each at a 2-sided 0.05 significance level for the comparison between CZP 200mg Q2W and placebo, will be performed in the sequence shown below. After the first test,

each subsequent test is performed only if the previous test is significant in favor of CZP at the 2-sided 0.05 level. Note that the first test relates to the primary efficacy variable while the others provide the sequence testing for secondary efficacy variables.

Has been changed to

The statistical analysis of the primary efficacy variable and selected secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure. The predefined order of hypothesis testing, each at a 2-sided 0.05 significance level for the comparison between CZP 200mg Q2W and placebo, will be performed in the sequence shown below. After the first test, each subsequent test is performed only if the previous test is significant in favor of CZP at the 2-sided 0.05 level. Note that the first test relates to the primary efficacy variable while the others provide the sequence testing for selected secondary efficacy variables.

Change #73

Section 14.3 Planned efficacy analyses

The primary efficacy variable measurement for this study is based on ASDAS-MI response at Week 52. The associated primary outcome of the study will be defined as a composite endpoint that is achieved if a subject fulfills the following 2 components:

1. Remain in the study and on study treatment through 52 weeks
2. Achieve an ASDAS-MI response at 52 weeks

For simplicity, this primary efficacy variable will be referred to as ASDAS-MI response at Week 52. However, the composite definition as described above will apply when this endpoint is analyzed. The primary analysis for this endpoint will be based on logistic regression. The odds ratio of the ASDAS-MI responder rates at Week 52 will be estimated and tested between treatment groups using a logistic regression model with factors of treatment group, region, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+). If the logistic regression model is unable to converge, then MRI/CRP classification may be dropped from the model to facilitate convergence. The study design is likely to result in some sites with a small number of enrolled subjects. The use of region as a stratification variable and as a factor in the model is intended to combine study centers in similar geographic regions. The geographic regions to be used will be defined in the IXRS and in the SAP. Given the composite endpoint definition described above, there will be no missing data for the primary endpoint, as subjects that discontinue study treatment prior to Week 52 or who do not have an ASDAS-MI status at Week 52 are considered nonresponders to study treatment.

As described in Section 6.3, subjects who discontinue study treatment will not necessarily be withdrawn from the study. In an attempt to minimize missing data, efforts will be made to continue to collect safety and efficacy data on these subjects through study completion. An alternative analysis for ASDAS-MI at Week 52 will be performed in which the observed data at Week 52 will be used, regardless of whether or not the subject is still on his/her randomized study treatment at that time. Despite efforts to continue to collect data on all subjects (even if they discontinue study treatment), there may still be subjects with missing data at Week 52. Such subjects will be considered as nonresponders in accordance with the composite endpoint

definition outlined above. The same logistic regression model specified for the primary analysis will be used.

Subgroup analyses by age, gender, race, symptom duration, smoking history, HLA-B27 genotype, anti-CZP Ab status, region, prior anti-TNF exposure, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) will be performed for the primary variable.

Has been changed to:

The primary efficacy variable measurement for this study is based on ASDAS-MI response at Week 52. The associated primary outcome of the study will be defined as a composite endpoint that is achieved if a subject fulfills the following 2 components:

1. Remain in the study and on the double-blind study treatment through 52 weeks
2. Achieve an ASDAS-MI response at 52 weeks

For simplicity, this primary efficacy variable will be referred to as ASDAS-MI response at Week 52. However, the composite definition as described above will apply when this endpoint is analyzed. The primary analysis for this endpoint will be based on logistic regression. The odds ratio of the ASDAS-MI responder rates at Week 52 will be estimated and tested between treatment groups using a logistic regression model with factors of treatment group, region, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+). If the logistic regression model is unable to converge, then the MRI/CRP classification variable may be dropped from the model to facilitate convergence. The study design is likely to result in some sites with a small number of enrolled subjects. The use of region as a stratification variable and as a factor in the model is intended to combine study centers in similar geographic regions. The geographic regions to be used will be defined in the IXRS and in the SAP. Given the composite endpoint definition described above, there will be no missing data for the primary endpoint, as subjects that discontinue the double-blind study treatment prior to Week 52 or who do not have an ASDAS MI status at Week 52 are considered nonresponders to the double-blind study treatment.

As described in Section 6.3, subjects who discontinue the double-blind study treatment will not necessarily be withdrawn from the study. In an attempt to minimize missing data, efforts will be made to continue to collect safety and efficacy data on these subjects through study completion. Sensitivity analyses will be performed to evaluate the impact of missing data on the analysis of the primary efficacy variable (see Section 14.8).

Subgroup analyses by age, gender, race, symptom duration, smoking history, HLA-B27 genotype, anti-CZP Ab status, region, prior anti-TNF exposure, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) will be performed for the primary efficacy variable. Subgroup analyses will be summarized using descriptive statistics only.

Change #74

Section 14.4 Secondary efficacy analyses

The changes from Baseline in BASDAI and BASFI at Week 12 and Week 52 are specified as secondary efficacy variables. As these are continuous variables, missing data must be handled using a different approach from what is specified for the primary efficacy endpoint (a responder variable).

Investigators will be given discretion to discontinue study treatment for subjects not responding in order to provide them with alternative therapy to treat the condition. Therefore, in many cases, missing efficacy data due to study treatment discontinuation should be dependent on the observed efficacy scores, but independent of unobserved data. This would be consistent with a missing at random pattern of missingness. However, the possibility of discontinuation due to tolerability or other unobserved data cannot be completely discounted. Therefore, a missing not at random mechanism will be considered as the primary analysis method of continuous secondary efficacy variables, where reference-based imputation methods will be used.

This approach will impute missing data as well as data at time points following discontinuation of study treatment for both the CZP and placebo groups using an imputation model developed based on data from the placebo group (Mallinckrodt, 2013). The estimand being evaluated in this case is a de-facto estimand that has been described as the difference in outcome improvement in all randomized subjects at the planned endpoint attributable to the initially randomized medication (Mallinckrodt, 2012). This reference-based imputation procedure will be described in greater detail in the SAP. The final model to be used on the imputed data will be an analysis of covariance (ANCOVA) model where response is the change from Baseline, with Baseline score as a fixed-effect covariate and treatment group, region, and MRI/CRP classification as fixed effect categorical factors.

Additionally, change from Baseline in SI joint SPARCC score at Week 12 is a continuous secondary efficacy variable. As with BASDAI and BASFI, a reference-based imputation approach will be used to account for missing data. However, it should be noted that, unlike BASDAI and BASFI, SPARCC score will not be measured at any time points between Baseline and Week 12, meaning that those are the only 2 time points that can be considered in the evaluation of SPARCC score at Week 12. Therefore, Week 12 represents the only time point at which the placebo treatment effect can be evaluated for the imputation procedure. Comparisons between treatment groups will be made using an ANCOVA on the imputed data set. The model will include Baseline score, treatment group, region, and MRI/CRP classification.

The ASAS40 response at Week 12 and Week 52 are responder secondary efficacy endpoints. As a responder variable, ASAS40 will be analyzed using logistic regression based on a model similar to the one described for the primary analysis. As with the primary efficacy endpoint, the ASAS40 will be treated as a composite endpoint when it is analyzed. Specifically, subjects will need to 1) achieve the relevant response (ASAS40) and 2) remain in the study and on their randomized study treatment through the time point being analyzed (Week 12 or Week 52).

The comparison of CZP 200mg Q2W to placebo as described above for the ASAS40 response, BASDAI, and BASFI at Week 12 and Week 52 and for SI joint SPARCC score at Week 12 will be part of the fixed sequence testing procedure outlined in Section 14.2.

Additionally, sensitivity analyses will be conducted on these secondary efficacy endpoints. In particular, the assumptions related to missing data will be investigated further. These analyses are described in Section 14.8.

An additional secondary efficacy variable is the number of subjects with relevant changes to background medication. This variable will be based on whether or not subjects take certain pre-specified background medications during the course of the study and will be defined in the

SAP. The analysis for this variable will use the same logistic regression model described for the primary variable.

Has been changed to:

The changes from Baseline in BASDAI and BASFI at Week 12 and Week 52 are specified as secondary efficacy variables. As these are continuous variables, missing data must be handled using a different approach from what is specified for the primary efficacy endpoint (a responder variable). In the current study, Investigators will be given discretion to discontinue the double blind study treatment for subjects not responding in order to provide them with alternative therapy to treat the condition. Therefore, in many cases, missing efficacy data due to the double-blind study treatment discontinuation should be dependent on the observed efficacy scores, but independent of unobserved data. This would be consistent with a missing at random (MAR) assumption. However, the possibility of discontinuation due to tolerability or other unobserved data cannot be completely discounted. Therefore, a missing not at random mechanism will be used for the analysis of continuous secondary efficacy variables.

A reference-based multiple imputation (MI) procedure will be used for this analysis, which will impute missing data as well as data at the time points following the discontinuation of the double-blind study treatment for both the CZP and placebo groups. This procedure will use an imputation model developed based on available data from the placebo group, thereby assuming a placebo trajectory for missing data following study treatment discontinuation for subjects in both treatment groups (Mallinckrodt, 2013). The estimand being evaluated in this case is the difference in the outcome of improvement in all randomized subjects at the planned endpoint, attributable to the initially randomized medication. This is an effectiveness estimand of the de facto hypothesis which has been referred to as "estimand 6" (Mallinckrodt, 2012).

Additionally, change from Baseline in SI joint SPARCC score at Week 12 is a continuous secondary efficacy variable. The same MI procedure specified as the main analysis approach for BASDAI and BASFI will be used to account for missing SPARCC data. However, it should be noted that, unlike BASDAI and BASFI, SPARCC score will not be measured at any time points between Baseline and Week 12, meaning that those are the only 2 time points that can be considered in the evaluation of SPARCC score at Week 12. Comparisons between treatment groups will be made using an ANCOVA model on the imputed data set. The model will include Baseline score, treatment group, region, and MRI/CRP classification.

The ASAS40 response at Week 12 and Week 52 are responder secondary efficacy endpoints. As a responder variable, ASAS40 will be analyzed using logistic regression based on a model similar to the one described for the primary analysis. As with the primary efficacy endpoint, the ASAS40 will be treated as a composite endpoint when it is analyzed. Specifically, subjects will need to 1) achieve the relevant response (ASAS40) and 2) remain in the study and on their randomized double-blind study treatment through the time point being analyzed (Week 12 or Week 52).

The comparison of CZP 200mg Q2W to placebo as described above for the ASAS40 response, BASDAI, and BASFI at Week 12 and Week 52 and for SI joint SPARCC score at Week 12 will be part of the fixed sequence testing procedure outlined in Section 14.2.

Additionally, sensitivity analyses will be conducted on these secondary efficacy endpoints. In particular, the assumptions related to missing data will be investigated further. These analyses are described in Section 14.8.

An additional secondary efficacy variable is the number of subjects with relevant changes to background medication. This variable will be based on whether or not subjects take certain pre-specified background medications during the course of the study and will be defined in the SAP. The analysis for this variable will use the same logistic regression model described for the primary variable.

Change #75

Section 14.5 Other efficacy analyses, paragraph 1

Treatment group comparisons for CZP 200mg Q2W vs placebo will be performed based on the change from Baseline in other selected efficacy variables. These analyses will be performed using an ANCOVA model including Baseline score, treatment group, region, and MRI/CRP classification. The treatment differences and corresponding 95% confidence intervals will be calculated based on the adjusted means. Missing values or values observed after discontinuing study treatment will be imputed using last observation carried forward (LOCF). The following variables will be analyzed in this manner:

Has been changed to:

Treatment group comparisons for CZP 200mg Q2W versus placebo will be performed based on the change from Baseline in other selected efficacy variables. These analyses will be performed using an ANCOVA model including Baseline score, treatment group, region, and MRI/CRP classification. The treatment differences and corresponding 95% confidence intervals will be calculated based on the adjusted means. Missing values or values observed after discontinuing the double-blind study treatment will be imputed using last observation carried forward (LOCF). The following variables will be analyzed in this manner:

Change #76

Section 14.6.1 Safety analyses, paragraph 2

Since subjects will be permitted to change background medications and because they may also discontinue study treatment and initiate a new treatment (including biologics) during the course of the study, special consideration will be given to how AEs are attributed to study treatment. This, along with other specialized AE summaries, will be described in greater detail in the SAP.

Has been changed to:

Since subjects will be permitted to change background medications and because they may also discontinue the double-blind study treatment and initiate a new treatment (including biologics) during the course of the study, special consideration will be given to how AEs are attributed to the double-blind study treatment. This, along with other specialized AE summaries, will be described in greater detail in the SAP.

Change #77

Section 14.6.2 Pharmacokinetic and immunogenicity variable analysis, paragraph 1

Certolizumab pegol plasma concentrations will be tabulated and summarized by treatment group (overall and by anti-CZP Ab level - above or below 2.4 units/mL within each treatment group) for each visit at which samples were taken using the geometric mean, geometric coefficient of variation, 95% confidence intervals (CIs), arithmetic mean, arithmetic SD, minimum and maximum, geomean plasma concentration time curves with their 95% CI will be plotted overall and by anti CZP Ab status.

Has been changed to:

Certolizumab pegol plasma concentrations will be tabulated and summarized by treatment group (overall and by anti-CZP Ab level - above or below 2.4 units/mL within each treatment group) for each visit at which samples were taken using the geometric mean, geometric coefficient of variation, 95% confidence intervals (CIs), arithmetic mean, arithmetic SD, minimum and maximum, geomean plasma concentration time curves with their 95% CI will be plotted overall and by anti CZP Ab status. Individual plasma concentrations for CZP and anti-CZP levels versus time will be produced on the same graph.

Change #78

Section 14.8 Handling of dropouts or missing data

For analysis purposes, the primary efficacy variable is defined as a composite endpoint in which it is necessary to achieve ASDAS-MI at Week 52 and to remain on randomized study treatment through Week 52 in order to be considered a responder (see Section 14.3). Because this composite endpoint definition does not allow for a missing response status, no formal method for handling missing data is needed in the primary analysis. An additional analysis (also described in Section 14.3) will be performed in which all observed data at Week 52 are used, including data collected for subjects who may have discontinued study treatment without being withdrawn from the study.

Analyses of other binary efficacy variables will be treated in the same way as the primary efficacy variable. That is, a subject will be considered a responder only if the response is achieved and if the subject is still on his/her randomized study treatment at the time when the variable is evaluated. For ASAS40 response at Week 12 and Week 52 (secondary efficacy endpoints included in the fixed sequence statistical testing procedure), an additional analysis based on all collected data (as described above for the primary endpoint) will be performed.

To account for missing data and data following discontinuation of study treatment for continuous secondary efficacy variables (change from Baseline in BASDAI and BASFI at Week 12 and Week 52 and change from Baseline in SI joint SPARCC score at Week 12), the analysis method that will be used when considering statistical significance in the fixed sequence testing procedure will be referenced-based imputation where an ANCOVA model is used on the multiply imputed data (see Section 14.4).

Other analyses of continuous secondary efficacy data will be implemented to evaluate sensitivity of results to the method of handling missing data and will include the following:

- ANCOVA based on all observed data (including from subjects who discontinued study treatment but continued in the study) where any remaining missing data is imputed using reference-based imputation methods
- mixed model for repeated measures (MMRM) with Baseline score as a fixed effect covariate and treatment group, region, MRI/CRP classification, and visits as fixed effect categorical factors, and Baseline by visit and treatment group by visit as interaction terms (where data following study treatment discontinuation are treated as missing)
- LOCF
- Baseline observation carried forward (BOCF)

Additionally, "tipping point" sensitivity analyses will be conducted. These analyses will vary assumptions about average outcomes among the subjects in the CZP treatment group who discontinue study treatment early through a series of delta adjustments (O'Kelly, 2014). These assumptions may be severe and will include the possibility that subjects with missing data in the CZP treatment group had worse outcomes than dropouts on the placebo arm. Such adjustments to the assumptions may be performed until a statistically significant result in favor of CZP is no longer observed. The plausibility of the assumptions leading to that change would then be considered. Further details on all of these sensitivity analyses will be provided in the SAP.

Descriptive summaries based on observed case data will also be prepared.

Additionally, algorithms for imputing missing or partial dates for safety evaluations will be detailed in the SAP.

Has been changed to:

For analysis purposes, the primary efficacy variable is defined as a composite endpoint in which it is necessary to achieve ASDAS-MI at Week 52 and to remain on randomized double-blind study treatment through Week 52 in order to be considered a responder (see Section 14.3). Because this composite endpoint definition does not allow for a missing response status, no formal method for handling missing data is needed in the primary efficacy analysis. However, in order to assess the impact of various missing data assumptions on the analysis, additional sensitivity analyses of the primary efficacy variable will be performed as follows:

- Including observed data at Week 52: The observed data at Week 52 will be used and analyzed according to randomized treatment, regardless of whether or not the subject is still on his/her randomized double-blind study treatment at that time. Despite efforts to continue to collect data on all subjects (even if they discontinue the double-blind study treatment), there may still be subjects with missing data at Week 52. Such subjects will be considered as non-responders in accordance with the composite endpoint definition outlined above. The same logistic regression model specified for the primary analysis will be used.
- MI: The MCMC method will be used to impute intermittent missing data. The resulting multiply imputed data sets will be monotone missing and will be imputed using monotone regression (assuming a MAR pattern). Note that the MI procedure will be done on the continuous ASDAS variable, which will be dichotomized for the logistic regression analysis. Ankylosing Spondylitis Disease Activity Score data collected following the discontinuation

of double-blind study treatment will be treated as missing in the original data set for this sensitivity analysis.

- Tipping point analysis: In this analysis, various assumptions will be made about average outcomes among the subsets of subjects who prematurely discontinued double-blind study treatment. Various "delta adjustments" will be made to the assumed responses among missing data in each treatment arm with varying degrees of plausibility (O'Kelly, 2014). The goal of the tipping point analysis is to identify assumptions about the missing data under which the conclusions change, ie, under which there is no longer evidence of a treatment effect. Then, the plausibility of such assumptions would be discussed. Further details of this procedure will be described in the SAP.
- Observed case analysis: This analysis will only include the observed data for subjects still on the original double-blind study treatment. Data collected after the discontinuation of double-blind study treatment and all other missing data will be excluded from the analysis. The same logistic regression model specified for the primary efficacy analysis will be performed.

The sensitivity analyses of the secondary binary efficacy variables (ASAS40 at Weeks 12 and 52) will be as follows:

- Including observed data at Week 52: As described for the primary efficacy variable.
- MI: As described for the primary efficacy variable. Note that as ASAS40 is a composite of 4 different variables, the MI procedure will be performed on each of these components, and the ASAS40 response will be derived based on the multiply imputed datasets.
- Reference-based MI: This procedure will impute missing data as well as data at the time points following the discontinuation of the double-blind study treatment for both the CZP and placebo groups. This procedure will use an imputation model developed based on data from the placebo group (Mallinckrodt, 2013). The estimand being evaluated in this case is the difference in the outcome of improvement in all randomized subjects at the planned endpoint, attributable to the initially randomized medication, which has been referred to as "estimand 6" (Mallinckrodt, 2012).
- Observed case analysis: As described for the primary efficacy variable.

The sensitivity analyses of secondary continuous efficacy variables (the change from Baseline in BASDAI and BASFI at Weeks 12 and 52 and the change from Baseline in the SI joint SPARCC score at Week 12) will be as follows:

- Including observed data at Week 52: As described for the primary efficacy variable.
- MI: As described for the primary efficacy variable.
- Observed case analysis: As described for the primary efficacy variable.
- LOCF

Missing data for the other efficacy variables described in Section 14.5 will be handled as follows:

- With imputation: Non-responder imputation for binary variables and LOCF for continuous variables (as described in Section 14.5)
- Observed case analysis: As described for the primary efficacy variable.

Additionally, algorithms for imputing missing or partial dates for safety evaluations will be detailed in the SAP.

Change #79

Section 14.10 Determination of sample size

Subjects will be randomized in a 1:1 ratio to the CZP 200mg Q2W and placebo treatment groups. The expected response rates for ASDAS-MI at Week 52 are 40% and 20% for CZP and placebo, respectively. A total sample size of 300 (150 subjects per treatment group) provides 95% power to detect a statistically significant difference in the ASDAS-MI response rate at Week 52 between CZP and placebo, using a 2-sided significance level of 0.05.

Has been changed to:

Subjects will be randomized in a 1:1 ratio to the CZP 200mg Q2W and placebo treatment groups. The expected responder rates for ASDAS-MI at Week 52 are 40% and 20% for CZP and placebo, respectively. A total sample size of 300 (150 subjects per treatment group) provides 95% power to detect a statistically significant difference in the ASDAS-MI responder rate at Week 52 between CZP and placebo, using a 2-sided significance level of 0.05.

Change #80

Section 17 References

Callhoff J, Sieper J, Weiß A, Zink A, Listing J. Efficacy of TNFα blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Ann Rheum Dis. 2015;

Has been changed to:

Callhoff J, Sieper J, Weiß A, Zink A, Listing J. Efficacy of TNFα blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Ann Rheum Dis. 2015;74:1241-8.

Change #81

Section 17 References

Dougados M, van der Heijde D, Sieper J, et al. Efficacy of etanercept in nonradiographic axial spondyloarthritis. The Symptomatic Efficacy and Effect on Objective Signs of Inflammation of Etanercept in Early Nonradiographic Axial Spondyloarthritis. Ann Rhuem. 2014;66:2091-102.

Has been changed to:

Dougados M, van der Heijde D, Sieper J, Braun J, Maksymowych W, Citera G, et al. Efficacy of etanercept in nonradiographic axial spondyloarthritis. The symptomatic efficacy and effect on objective signs of inflammation of etanercept in early nonradiographic axial spondyloarthritis. Ann Rhuem. 2014;66:2091-102.

Change #82

Section 17 References

van Tubergen A, Black PM, Coteur G. Are Patient-Reported Outcome Instruments for Ankylosing Spondylitis Fit-For-Purpose for the Axial Spondyloarthritis Patient? A Qualitative and Psychometric Analysis. Rheum. In press

Has been changed to:

van Tubergen A, Black PM, Coteur G. Are Patient-Reported Outcome Instruments for Ankylosing Spondylitis Fit-For-Purpose for the Axial Spondyloarthritis Patient? A Qualitative and Psychometric Analysis. Rheum. 2015;54:1842-51.

Change #83

Section 17 References

Weber U, Ostergaard M, Lambert RG, Pedersen SJ, Chan SM, Zubler V, et al. Candidate lesion- based criteria for defining a positive sacroiliac joint MRI in two cohorts of patients with axial spondyloarthritis. Ann Rheum Dis. 2014-205408. Doi: 10.1136/annrheumdis-2014-205408,

Has been changed to:

Weber U, Ostergaard M, Lambert RG, Pedersen SJ, Chan SM, Zubler V, et al. Candidate lesion based criteria for defining a positive sacroiliac joint MRI in two cohorts of patients with axial spondyloarthritis. Ann Rheum Dis. 2015;74:1976-82.

Change #84

Section 18.1 ASAS classification criteria for axial SpA, footnote 3 (number 1)

1) age at onset <40 years

Has been changed to:

1) age at onset <45 years

Change #85

Sections 18.9 PGADA (NRS) and 18.11 Total spinal pain NRS and nocturnal spinal pain NRS; "Spondylitis" has been changed to "Spondyloarthritis".

18.14 Protocol Amendment 2

Rationale for the amendment

This substantial amendment includes changes to clarify some of the study procedures, as well as to update Inclusion Criteria 5 and 6 concerning the Assessment of SpondyloArthritis International Society (ASAS) criteria, and to increase the number of participating sites and screened subjects. The rationale for the changes is as follows:

- Inclusion Criterion 5 about subjects having a documented diagnosis of adult-onset axial spondyloarthritis (axSpA) as defined by the specified ASAS criteria has been updated in order to: i.) clarify that the ASAS criteria are classification criteria and are not intended to be used as diagnosis criteria and to avoid any misinterpretation, and ii.) remove the part "with at least 12 months symptom duration before Screening" since this part has been added to the updated Inclusion Criterion 6.
- Inclusion Criterion 6 about subjects having evidence of inflammatory back pain as defined by the ASAS criteria has been updated to specify that subjects must have had back pain for at least 12 months before Screening. The reason is that the requirements for objective signs and symptoms of inflammation are clearly defined in Inclusion Criterion 9. The initial Inclusion Criterion 6 was therefore a repetition of this requirement. The updated version stresses the importance of having back pain as the lead symptom for axSpA for at least 12 months to ensure that the pain is chronic in nature.
- The number of participating sites and the number of screened subjects have been increased from 95 to 120 and from 900 to 1200, respectively, in order to adjust for a higher screening failure rate, which was actually exceeding the expected rate of 67%.
- Other changes included the following:
  - Text about chest x-ray at Screening has been updated to clarify that the chest x-ray must be done at Screening unless a chest x-ray (or a computed tomography of the chest) has been done within 3 months prior to the Screening visit.
  - Text about study treatment administration at on-site visits has been updated to clarify at which visits the subcutaneous (sc) injections will be administered by dedicated, unblinded, and adequately trained site personnel or by self-injection of the subject under the supervision of the unblinded study personnel.
  - Study contact information for Clinical Trial Biostatistician has been updated.
  - Minor editorial changes have been made.

Modifications and changes

Global changes

The following changes were made:

- The study contact information for Clinical Trial Biostatistician has been updated.
- Inclusion Criteria 5 and 6 have been updated.

- The number of participating sites and screened subjects has been increased from 95 to 120 and from 900 to 1200, respectively.
- Text about chest x-ray at Screening has been updated throughout the protocol to clarify that the chest x-ray must be done at Screening unless a chest x-ray (or a computed tomography of the chest) has been done within 3 months prior to the Screening visit.
- Text about study treatment administration at on-site visits has been updated to clarify at which visits the sc injections will be administered by dedicated, unblinded, and adequately trained site personnel or by self-injection of the subject under the supervision of the unblinded study personnel.
- Other changes made in this amendment are to provide clarification or are administrative in nature, including minor editorial changes to abbreviations.

Specific changes

This section displays the modifications in this amendment compared with the Final Protocol Amendment 1 dated 15 Dec 2015. The changes are displayed in order of appearance.

Change #1

Study Contact Information

Clinical Trial Biostatistician

Name:	[redacted], MS
Address:	[redacted]
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Clinical Trial Biostatistician

Name:	[redacted], MS
Address:	[redacted]
Phone:	[redacted]
Fax:	[redacted]

Change #2

Section 1 Summary, paragraph 2

The study population will be subjects (≥18 years), with a documented diagnosis of adult-onset axSpA as meeting the Assessment of SpondyloArthritis International Society ([ASAS], Sieper et al, 2009) criteria of at least 12 months' symptom duration, and with active disease defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and spinal pain ≥4 on a 0 to 10 Numerical Rating Scale (NRS). At Baseline, evidence of inflammatory disease will be confirmed either by presence of sacroiliitis on MRI (according to ASAS/Outcome Measures in Rheumatology Clinical Trials [OMERACT] criteria) or by elevated CRP or by presence of both.

Has been changed to:

The study population will be subjects (≥18 years), with a documented diagnosis of adult-onset axSpA and who meet the Assessment of SpondyloArthritis International Society ([ASAS], Sieper et al, 2009) criteria for axSpA, who have had back pain of at least 12 months' symptom duration, and with active disease defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and spinal pain ≥4 on a 0 to 10 Numerical Rating Scale (NRS). At Baseline, evidence of inflammatory disease will be confirmed either by presence of sacroiliitis on MRI (according to ASAS/Outcome Measures in Rheumatology Clinical Trials [OMERACT] criteria) or by elevated CRP or by presence of both.

Change #3

Section 1 Summary, paragraph 4

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site by dedicated, unblinded, and adequately trained site personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. All subjects will receive training for self injection at the study site at Weeks 10 and 12. During the training at the Weeks 10 and 12 visits, the double-blind study treatment will be self administered under the supervision of the dedicated unblinded study personnel.

Has been changed to:

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site. At the Week 0, 2, 4, 6, and 8 visits, the administration must be done by dedicated, unblinded, and adequately trained site personnel. At the Week 10 and 12 visits, the subject will receive training on self-injection and the study treatment will be self-administered under the supervision of the unblinded study personnel. At Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50, the study treatment administration should preferably be done by the unblinded study personnel, or alternatively by self-injection of the subject under the supervision of the unblinded study personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46.

Change #4

Section 1 Summary, paragraph 16, first sentence

Approximately 900 subjects will be screened in order to have 300 subjects (150 subjects per treatment group) randomized into the study.

Has been changed to:

Approximately 1200 subjects will be screened in order to have 300 subjects (150 subjects per treatment group) randomized into the study.

Change #5

Section 4.4 Safety variables, paragraph 6

At Screening, all subjects will have an Interferon-Gamma Release Assay (IGRA) test (QuantiFERON® TB test or Elispot® test, when the QuantiFERON test indicated is not available), and a chest x-ray read (or, if done, computed tomography of the chest) which must be reported consistent with standard clinical reporting practice by an experienced qualified TB specialist, radiologist, or a pulmonologist, who is specifically required to look for signs of active TB or signs of past/inactive TB infection. The official report of the imaging must specifically indicate the absence of findings suggestive of current active TB or prior inactive TB. In addition to a physical examination done intermittently throughout the study, subjects will be evaluated at Screening, Baseline, and every 12 weeks thereafter up to and including the Week 52/WD visit, for signs and symptoms of latent tuberculosis (LTB) or active TB infection and risk factors for exposure to TB using the TB questionnaire.

Has been changed to:

At Screening, all subjects will have an Interferon-Gamma Release Assay (IGRA) test (QuantiFERON® TB test or Elispot® test, when the QuantiFERON test indicated is not available), and a chest x-ray reading (or, if done, computed tomography of the chest) which must be reported consistent with standard clinical reporting practice by an experienced qualified TB specialist, radiologist, or a pulmonologist, who is specifically required to look for signs of active TB or signs of past/inactive TB infection. A chest x-ray will not be done at Screening if a chest x-ray (or computed tomography of the chest) was done within 3 months prior to the Screening visit. The official report of the imaging must specifically indicate the absence of findings suggestive of current active TB or prior inactive TB. In addition to a physical examination done intermittently throughout the study, subjects will be evaluated at Screening, Baseline, and every 12 weeks thereafter up to Week 36 and including the Week 52/WD visit, for signs and symptoms of latent tuberculosis (LTB) or active TB infection and risk factors for exposure to TB using the TB questionnaire.

Change #6

Section 5.1.1 Study periods, Period 2, paragraph 2

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site by dedicated, unblinded and adequately trained site personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. All subjects will receive training for

self-injection at the study site on Weeks 10 and 12. During the training on Weeks 10 and 12 visits, the double-blind study treatment will be self-administered under the supervision of the unblinded study personnel. Concomitant medications permitted during the study should remain stable for at least 4 weeks prior to the Weeks 12, 24, and 52/WD assessments.

Has been changed to:

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site. At the Week 0, 2, 4, 6, and 8 visits, the administration must be done by dedicated, unblinded, and adequately trained site personnel. At the Week 10 and 12 visits, the subject will receive training on self-injection and the study treatment will be self-administered under the supervision of the unblinded study personnel. At Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50, the study treatment administration should preferably be done by the unblinded study personnel, or alternatively by self-injection of the subject under the supervision of the unblinded study personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. Concomitant medications permitted during the study should remain stable for at least 4 weeks prior to the Weeks 12, 24, and 52/WD assessments.

Change #7

Section 5.1.3 Planned number of subjects and site(s)

Approximately 900 subjects are expected to enter the Screening Period in order to have 300 subjects randomized into the Double-Blind Period. The end of the study will be defined as the date of last subject last FU visit. It is planned to enroll the subjects at approximately 95 sites.

Has been changed to:

Approximately 1200 subjects are expected to enter the Screening Period in order to have 300 subjects randomized into the Double-Blind Period. The end of the study will be defined as the date of last subject last FU visit. It is planned to enroll the subjects at approximately 120 sites.

Change #8

Section 5.2 Schedule of study assessments - Study Periods 1 to 3 (Screening until FU), Table 5-1: footnote j

[j] Screening chest x-ray (or computed tomography of the chest) must have occurred within 3 months prior to Screening visit and will be repeated at Week 52/WD visit only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure).

Has been changed to:

[j] A chest x-ray must be done at Screening unless a chest x-ray (or computed tomography of the chest) has been done within 3 months prior to the Screening visit. The chest x-ray will be repeated at Week 52/WD visit only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure).

Change #9

Section 5.2 Schedule of study assessments - Study Periods 1 to 3 (Screening until FU), Table 5-1: footnote q

[q] At on-site visit days (Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site by dedicated, unblinded and adequately trained site personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. From Week 52 onwards, after completion of all onsite assessments and procedures, the subject may receive open-label CZP at the discretion of the Investigator.

Has been changed to:

[q] At on-site visit days (Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site. At the Week 0, 2, 4, 6, and 8 visits, the administration must be done by dedicated, unblinded, and adequately trained site personnel. At the Week 10 and 12 visits, the subject will receive training on self-injection and the study treatment will be self-administered under the supervision of the unblinded study personnel. At Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50, the study treatment administration should preferably be done by the unblinded study personnel, or alternatively by self-injection of the subject under the supervision of the unblinded study personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. From Week 52 onwards, after completion of all onsite assessments and procedures, the subject may receive open-label CZP at the discretion of the Investigator.

Change #10

Section 6.1 Inclusion criteria, Inclusion Criteria 5 and 6

5. Subjects must have a documented diagnosis of adult-onset axSpA as defined by the specified ASAS criteria (not including family history and good response to NSAIDs; see Appendix 18.1) with at least 12 months symptom duration before Screening.
6. Subjects must have evidence of inflammatory back pain as defined by the ASAS criteria.

Have been changed to:

5. Subjects must have a documented diagnosis of adult-onset axSpA and meet the ASAS criteria for axSpA (not including family history and good response to NSAIDs; see Appendix 18.1).
6. Subjects must have had back pain for at least 12 months before Screening.

Change #11

Section 7.2.1 Treatment administration, paragraph 2

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site by dedicated, unblinded, and adequately trained site personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46. All subjects will receive training for self-injection at the study site on Weeks 10 and 12. During the training on Weeks 10 and 12

visits, the double-blind study treatment will be self-administered under the supervision of the unblinded study personnel.

Has been changed to:

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments will be administered sc at the study site. At the Week 0, 2, 4, 6, and 8 visits, the administration must be done by dedicated, unblinded, and adequately trained site personnel. At the Week 10 and 12 visits, the subject will receive training on self-injection and the study treatment will be self-administered under the supervision of the unblinded study personnel. At Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50, the study treatment administration should preferably be done by the unblinded study personnel, or alternatively by self-injection of the subject under the supervision of the unblinded study personnel. The double-blind study treatment will be self-injected at home at Weeks 14, 18, 22, 26, 30, 34, 38, 42, and 46.

Change #12

Section 8.1 Screening visit (Week -6 to Day -1), bullet 8

- Chest x-ray (must occur within 3 months prior to Screening visit)

Has been changed to:

- Chest x-ray to be done at Screening (unless a chest x-ray or computed tomography of the chest has been done within 3 months prior to the Screening visit)

Change #13

Section 12.6.3.2 Chest x-ray

A plain posteroanterior chest x-ray (or, if done, computed axial tomography of the chest) must be done within 3 months prior to the Screening visit. The chest x-ray must be clear of signs of TB infection (previous or current) before first study drug administration. The chest x-ray will be repeated at Week 52/WD visit (if chest x-ray was performed more than 12 weeks prior to Week 52/WD visit), only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

The chest x-ray (or, if done, Computed Axial Tomography of the Chest) must be negative for TB infection as determined by a qualified radiologist and/ or pulmonary physician. Any new clinically significant findings post-Baseline during physical exam or on chest x-ray must be documented in the source documents and CRF as an AE.

Has been changed to:

A plain posteroanterior chest x-ray must be done at Screening unless a chest x-ray (or a computed tomography of the chest) has been done within 3 months prior to the Screening visit. The chest x-ray must be clear of signs of TB infection (previous or current) before first study

drug administration. The chest x-ray will be repeated at Week 52/WD visit (if chest x-ray was performed more than 12 weeks prior to Week 52/WD visit), only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

The chest x-ray (or, if done, the computed tomography of the chest) must be negative for TB infection as determined by a qualified radiologist and/ or pulmonary physician. Any new clinically significant findings post-Baseline during physical exam or on chest x-ray must be documented in the source documents and CRF as an AE.

18.15 Protocol Amendment 3

Rationale for the amendment

This substantial amendment includes changes to clarify the study details regarding the additional 2 years of long-term, open-label CZP treatment that will be provided to eligible subjects at the completion of the Week 52 visit. This period of the study has been named the Safety-Follow Up Extension (SFE) Period and the protocol has been updated throughout accordingly (eg, a new Schedule of Study Assessments has been added and eligibility criteria, guidance for study drug administration and concomitant medication usage have been updated).

Additional changes include:

- allowing female subjects who become pregnant while participating in the AS0006 study the option to enroll in a separate, observational, pregnancy follow-up study sponsored by UCB.
- removal of the 40% cap on IXRS randomization to each of the 3 clinical subgroups for MRI/CRP classifications: (MRI+/CRP+, MRI+/CRP-, or MRI-/CRP+) in order to reflect the real world situation.
- to clarify that cases of potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of interest (ie, without waiting for any additional etiologic investigations to have been concluded).
- minor typographical errors have been corrected throughout the protocol. Additional specific changes are listed below.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

Specific changes

Change #1

The study acronym (C-AXSPAND) was added to the title page.

Change #2

The fax number for SAE reporting in the USA and Canada has been updated.

Serious Adverse Event reporting (24h) and safety related issues	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **USA and Canada:** +1 800 880 6949 or +1 866 890 3175
E-Mail	**DS_ICT@ucb.com**

Change #3

List of abbreviations

The following terms were revised or added:

ICH	International Council for Harmonisation
SFE	Safety Follow-Up Extension
SFE-SS	Safety Follow-Up Extension-Safety Set

Change #4

Section 1 Summary

Paragraph 1, first sentence:

AS0006 is a randomized, double-blind, parallel-group, placebo-controlled study, consisting of 52 weeks of treatment with certolizumab pegol (CZP) and a Follow-Up (FU) Period of 8 weeks after the Week 52 visit.

Has been changed to:

The C-axSpAnd study (AS0006) is a randomized, double-blind, parallel-group, placebo-controlled study, consisting of 52 weeks of treatment with certolizumab pegol (CZP) and a Follow-Up (FU) Period of 8 weeks after the Week 52 visit.

And paragraphs 6 and 7:

Subjects whose disease activity cannot be controlled by study medication and changes in background therapy (including and not limited to analgesics, NSAIDs, and slow-acting antirheumatic drugs [SAARDs]) will be permitted to withdraw from the double-blind study drug. Subjects will either transition to open-label CZP treatment offered by UCB or to other treatment (including biologics) at the discretion of the Investigator until the assessment of the primary endpoint at Week 52. At the completion of the Week 52 visit, and in accordance with the local regulatory requirements, CZP will be provided for a maximum duration of 2 years or until marketing authorization is granted for CZP (if applicable), whichever comes first.

All subjects, including those withdrawn from double-blind study treatment, will have a FU visit 8 weeks after their final Week 52 visit.

Have been changed to:

Subjects whose disease activity cannot be controlled by study medication and changes in background therapy (including and not limited to analgesics, NSAIDs, and slow-acting antirheumatic drugs [SAARDs]) will be permitted to withdraw from the double-blind study drug. Subjects will either transition to open-label CZP treatment offered by UCB or to other treatment (including biologics) at the discretion of the Investigator until the assessment of the primary endpoint at Week 52. At the completion of the Week 52 visit assessments, subjects on double-blind study treatment may receive open-label CZP treatment for an additional 2 years in an open-label, Safety Follow-Up Extension (SFE) Period. Subjects who withdrew from double-blind study treatment and transitioned to open-label CZP treatment are also eligible to participate in the SFE Period after completing the Week 52 visit assessments. Subjects on alternative treatments are not eligible to participate in the SFE Period.

All subjects not participating in the SFE Period after study completion at Week 52, including those withdrawn from the study prematurely, will have a FU visit 8 weeks after their Week 52 visit.

And paragraphs 15, 16, and 17:

Safety variables to be assessed are adverse events (AEs), vital signs, physical examination, and measurements of laboratory parameters. In addition, subjects will be evaluated at Screening, Baseline, and at every 12 weeks thereafter up to Week 36 and including Week 52/Withdrawal (WD) for signs and symptoms of latent or active tuberculosis (TB) infection and risk factors for exposure to TB using the TB questionnaire.

Approximately 1200 subjects will be screened in order to have 300 subjects (150 subjects per treatment group) randomized into the study. Randomization will be stratified by presence of sacroiliitis on MRI and elevated CRP to ensure balanced treatment allocation across 3 subgroups: MRI+/CRP+; MRI+/CRP-; MRI-/CRP+. For each subject, the study will last a maximum of 66 weeks and will consist of 3 periods:

- Screening Period lasting up to 6 weeks
- Double-Blind, Placebo-Controlled Period for 52 weeks
- FU Period 8 weeks after the Week 52/WD visit.

The estimated recruitment period is up to 15 months. The first subject first visit is planned in Quarter 3 2015. A completed subject is one who completes the Week 52 visit.

Have been changed to:

Safety variables to be assessed are adverse events (AEs), vital signs, physical examination, and measurements of laboratory parameters. In addition, subjects will be evaluated at Screening, Baseline, and at every 12 weeks thereafter up to Week 36 and including Week 52/Withdrawal (WD) (for subjects not participating in the SFE Period) for signs and symptoms of latent or active tuberculosis (TB) infection and risk factors for exposure to TB using the TB questionnaire.

Approximately 1200 subjects will be screened in order to have 300 subjects (150 subjects per treatment group) randomized into the study. Randomization will be stratified by presence of sacroiliitis on MRI and elevated CRP to ensure balanced treatment allocation across 3 subgroups: MRI+/CRP+; MRI+/CRP-; MRI-/CRP+.

For each subject, the study will consist of 3 periods and will last a maximum of 66 weeks:

- Screening Period lasting up to 6 weeks
- Double-Blind, Placebo-Controlled Period for 52 weeks
- FU Period 8 weeks after the Week 52/WD visit (for subjects not participating in the SFE Period).

For subjects participating in the SFE Period, the study will extend up to a maximum of 104 additional weeks.

The estimated recruitment period is up to 15 months. The first subject first visit is planned in Quarter 3 2015. The end of the study will be defined as the date of the last subject's last visit,

defined as the FU visit 8 weeks after the Week 52/WD visit for subjects not participating in the SFE Period, or the last visit of the SFE Period.

Change #5

Section 2.5 Rationale

Paragraph 2:

To address the unmet need for treatment options for nr-axSpA, AS0006 will be conducted focusing on subjects who do not meet the mNY classification criteria for AS (see Appendix 18.2). Data suggest that patients with objective signs of inflammation and high disease activity are likely to run a chronic disease course and unlikely to be well managed on conventional therapy (Rudwaleit ACR 2013). Furthermore, studies where anti-TNFs have been withdrawn in nr-axSpA patients show that patients flare quickly and hence the disease is unlikely to go into spontaneous remission. However, there are no long-term prospective studies to assess how patients meeting the ASAS classification criteria respond to conventional therapies. With the conduct of this 52-week study comparing CZP to placebo in combination with standard of care, a better understanding should be gained of how a long-term anti-TNF therapy compares to standard of care in patients meeting the ASAS criteria with objective signs of inflammation. Moreover, patients whose disease cannot be managed under the blinded study treatment conditions will be able to discontinue the double-blind study treatment and transition to either open-label CZP or other therapies.

Has been changed to:

To address the unmet need for treatment options for nr-axSpA, AS0006 will be conducted focusing on subjects who do not meet the mNY classification criteria for AS (see Appendix 18.2). Data suggest that patients with objective signs of inflammation and high disease activity are likely to run a chronic disease course and unlikely to be well managed on conventional therapy (Rudwaleit ACR 2013). Furthermore, studies where anti-TNFs have been withdrawn in nr-axSpA patients show that patients flare quickly and hence the disease is unlikely to go into spontaneous remission. However, there are no long-term prospective studies to assess how patients meeting the ASAS classification criteria respond to conventional therapies. With the conduct of the 52-week blinded study period comparing CZP to placebo in combination with standard of care, a better understanding should be gained of how a long-term anti-TNF therapy compares to standard of care in patients meeting the ASAS criteria with objective signs of inflammation. Moreover, patients whose disease cannot be managed under the blinded study treatment conditions will be able to discontinue the double-blind study treatment and transition to either open-label CZP or other therapies.

And a new 3rd paragraph has been added:

The addition of the SFE Period will allow collection of long-term safety data from eligible subjects on open-label CZP for up to 2 years. During the SFE Period, CZP will be provided by the Sponsor. The treating investigator is requested to apply routine, standard of care according to local standard medical practice and investigator clinical judgment.

Change #6

Section 5.1 Study description

Paragraph 1:

Study AS0006 is a 52-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study to evaluate the efficacy and safety of CZP in adult subjects with active axSpA without x-ray evidence of AS and with objective signs of inflammation (sacroiliitis on MRI and/or elevated CRP) and who have had an inadequate response to, have a contraindication to, or are intolerant to NSAIDs.

Has been changed to:

Study AS0006 is a 52-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study to evaluate the efficacy and safety of CZP in adult subjects with active axSpA without x-ray evidence of AS and with objective signs of inflammation (sacroiliitis on MRI and/or elevated CRP) and who have had an inadequate response to, have a contraindication to, or are intolerant to NSAIDs. At the completion of the Week 52 visit assessments, eligible subjects may receive open-label CZP treatment for an additional 2 years in an open-label, SFE Period.

Change #7

Section 5.1.1 Study periods

The subsection describing the Follow-Up Period (Period 3):

Period 3 (Follow-Up Period):

All subjects, including those withdrawn from the double-blind study treatment, will have a FU visit 8 weeks after the Week 52/WD visit.

Has been changed to:

Period 3 (Follow-Up Period):

All subjects not participating in the SFE Period after Week 52, including those withdrawn from the study prematurely, will have a FU visit 8 weeks after the Week 52/WD visit.

And a new subsection describing the SFE Period has been added:

Safety Follow-Up Extension (SFE) Period: Week 52 to Week 156, open-label.

At the completion of the Week 52 visit assessments, subjects on double-blind study treatment may receive open-label CZP treatment for an additional 2 years. Subjects who withdrew from double-blind study treatment and transitioned to open-label CZP treatment are also eligible to participate in the SFE Period after completing the Week 52 visit assessments. Subjects on alternative treatments are not eligible to participate in the SFE Period.

Eligible subjects are allowed to roll-over to the SFE-Period up to 3 months after completion of the Week 52 assessments.

In order to maintain the blind for subjects completing double-blind treatment, their study treatment will be administered sc at the study site by unblinded, dedicated study personnel on Weeks 52, 54, and 56. Subjects who withdrew from double-blind study treatment and

transitioned to open-label CZP treatment do not need to visit the site at Week 54 and Week 56, and should continue their open-label CZP treatment regimen.

For the remainder of the SFE Period, CZP can be administered at the site by dedicated study personnel, or by self-injection of the subject under the supervision of the dedicated study personnel, or subjects may self-administer their study treatment Q2W at home.

Starting at Week 64, all subjects are to visit the site approximately every 12 weeks for assessments.

The last dosing visit will be at Week 154. The final study assessments are performed at Week 156.

Change #8

Section 5.1.2 Study duration per subject

For each subject, the study will last a maximum of 66 weeks, as follows:

- Up to 6 weeks in the Screening Period
- 52 weeks in the Double-Blind Period
- A FU visit 8 weeks after the Week 52/WD visit

The estimated recruitment period is up to 15 months. The first subject first visit is planned in Quarter 3 of 2015. A completed subject is one who completes the Week 52/WD visit. Subjects will either transition to open-label CZP treatment offered by UCB or to other treatment (including biologics) at the discretion of the Investigator until the assessment of the primary endpoint at Week 52/WD. At the completion of the Week 52/WD visit, and in accordance with the local regulatory requirements, CZP will be provided for a maximum duration of 2 years or until marketing authorization is granted for CZP (if applicable), whichever comes first.

Has been changed to:

For each subject, the first 3 periods of the study will last a maximum of 66 weeks, as follows:

- Up to 6 weeks in the Screening Period
- 52 weeks in the Double-Blind Period
- A FU visit 8 weeks after the Week 52/WD visit (for subjects not participating in the SFE Period).

For subjects participating in the SFE Period, the study will extend up to a maximum of 104 additional weeks.

The estimated recruitment period is up to 15 months. The first subject first visit is planned in Quarter 3 of 2015. The end of the study will be defined as the date of the last subject's last visit, defined as the FU visit 8 weeks after the Week 52/WD visit for subjects not participating in the SFE Period, or the last visit of the SFE Period

Change #9

Section 5.2 Schedule of study assessments

The Schedule of assessments is shown in Table 5-1 for subjects who complete the study on either CZP 200mg Q2W or placebo.

In order to optimize the treatment the Investigator may adjust the background medication in accordance with the specifications described in Table 7–1.

At any time during the study course, but preferably not before Week 12, the Investigator may discontinue the double-blind study treatment and start open-label treatment with either CZP (which will be provided free of charge by UCB) or an alternative drug (eg, other treatment [including biologics]). Table 5–2 shows the schedule of assessments for subjects receiving open-label treatment with CZP and Table 5–3 shows the schedule of assessments for subjects receiving an alternative treatment (not CZP).

Has been changed to:

The Schedule of assessments is shown in Table 5-1 for subjects who complete 52 weeks of treatment on either CZP 200mg Q2W or placebo.

In order to optimize the treatment the Investigator may adjust the background medication in accordance with the specifications described in Table 7-1.

At any time during the study course, but preferably not before Week 12, the Investigator may discontinue the double-blind study treatment and start open-label treatment with either CZP (which will be provided free of charge by UCB) or an alternative drug (eg, other treatment [including biologics]). Table 5-2 shows the schedule of assessments for subjects receiving open-label treatment with CZP and Table 5-3 shows the schedule of assessments for subjects receiving an alternative treatment (not CZP).

Table 5-6 shows the schedule of assessments for subjects participating in the SFE Period.

Change #10

The title of Table 5-1:

Table 5–1: Schedule of study assessment –– Study Periods 1 to 3 (Screening until FU)

Has been changed to:

Table 5–1: Schedule of study assessments –– Screening through Week 52 and FU

And the visit number, 29, has been removed from the column of assessments to be performed at the Follow-Up Visit.

And the following note has been added under the table:

Note: At the completion of the Week 52 visit, subjects may receive open-label CZP treatment for an additional 2 years in the SFE Period.

And footnote b under Table 5-1:

[b] FU: 8 weeks after Week 52/WD visit.

Has been changed to:

[b] FU: 8 weeks after Week 52/WD visit for subjects not participating in the SFE.

And footnote k under Table 5-1:

[k.] TB test: IGRA test (QuantiFERON test [or Elispot test when the QuantiFERON indicated is not available]). The TB test will be repeated at Week 52 (or at WD visit if medically indicated) for subjects with previously negative TB test result. Subjects who tested positive for TB should be encouraged to complete a FU visit (8 weeks after the Week 52/WD visit) and follow-up information of suspected and confirmed TB cases should be provided to UCB at least after 3, 9, and 12 months of the start date of anti-TB treatment.

Has been changed to:

[k] TB test: IGRA test (QuantiFERON test [or Elispot test when the QuantiFERON indicated is not available]). The TB test will be repeated at Week 52 (or at WD visit if medically indicated) for subjects with previously negative TB test result. Subjects who tested positive for TB should be encouraged to complete a FU visit (8 weeks after the Week 52/WD visit for subjects not participating in the SFE) and follow-up information of suspected and confirmed TB cases should be provided to UCB at least after 3, 9, and 12 months of the start date of anti-TB treatment.

Change #11

Table 5–2: Schedule of alternative study assessment with CZP - after subject discontinuation of the double blind study treatment

The following note has been added under the table:

Note: At the completion of the Week 52 visit, subjects who transitioned to open-label CZP treatment after withdrawal from the Double-Blind Period are eligible to participate in the SFE Period.

And footnote a of Table 5-2:

[a] FU: 8 weeks after Week 52/WD visit.

Has been changed to:

[a] FU: 8 weeks after Week 52/WD visit for subjects not participating in the SFE Period.

Change #12

Table 5–3: Schedule of alternative study assessment with other treatment (including biologics) - after subject discontinuation of the double-blind study treatment

Pregnancy testing has been added to the table with the following footnote g:

[g] Pregnancy testing must be carried out for women of childbearing potential and will be a serum test at the FU visit and a urine test (dipstick) at wdt Week 0 and Week 52/WD visit.

Change #13

A Schedule of assessments for the SFE Period (Table 5-6) has been added:

Table 5–6: Schedule of study assessments - Safety Follow-Up Extension Period

Visit #	29	30	31	32	33	34	35	36	37	38	39	40
Overall Study Week/SFE Week Protocol Activity	**52/0**[a]	**54/2**	**56/4**	**64/12**	**76/24**	**88/36**	**100/48**	**112/60**	**124/72**	**136/84**	**148/96**	**156/104/WD**
Informed consent[b]	X											
AEs		X	X	X	X	X	X	X	X	X	X	X
IXRS[c]	X	**X**	**X**	X	X	X	X	X	X	X	X	X
Study drug loading dose administration sc[d]	X	X	X									
Study drug dispensation[e]	X			X	X	X	X	X	X	X	X	

AEs=adverse events; CZP=certolizumab pegol; FU=Follow-Up; IXRS=Interactive Response System; SFE=Safety Follow-Up Extension; WD=Withdrawal;

[a] Assessments performed at the Week 52 Visit for subjects who completed the previous Double-Blind Period are in Table 5–1; Assessments performed at the Week 52 Visit for subjects who transitioned to open-label CZP treatment after withdrawal from the Double-Blind Period are in Table 5–2.

[b] A separate informed consent form will be obtained from subjects consenting to participate in the SFE Period.

[c] Contact IXRS to register the visit and obtain next kit number, where applicable, or to indicate that the subject has completed the SFE Period or withdrawn from the study.

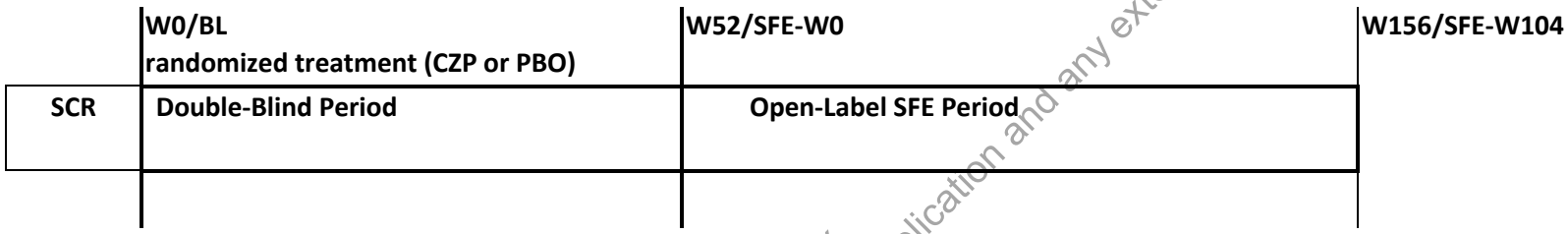
[d] At Weeks 52, 54, and 56, study treatment administration should be performed at the site by unblinded study personnel in order to keep the blind (see Section 7.2.1).

[e] Starting at Week 52 for subjects completing open-label CZP treatment and the Week 52 visit, dispense the assigned study medication to the subject for use at home, as appropriate.

Change #14

A new schematic diagram for the SFE Period (Figure 5-3) has been added:

Figure 5-3: Schematic diagram for subjects completing the double-blind study treatment and rolling over to the SFE Period



BL=Baseline; CZP=certolizumab pegol; FU=Follow-Up; SFE=Safety Extension; PBO=placebo; SCR=Screening; SFE=safety Follow-Up Extension; W=week

Note: Subjects who complete either double-blind treatment or open-label CZP-treatment and all assessments at Week 52 are eligible to roll-over to the SFE Period. Subjects who complete alternative treatment must finish the study at Week 52 and be scheduled for the final FU visit (8 weeks after the Week 52 visit).

Change #15

Section 5.4 Rationale for study design and selection of dose

Paragraph 2:

In accordance with prescribing information for CZP, 3 loading doses of 400mg Q2W should be administered upon initiation of therapy. Thus all subjects who transition to open-label CZP within the AS0006 study from the Double-Blind Period will receive this loading dose prior to the maintenance dose of 200mg Q2W. It is recognized that some subjects would have been on active CZP prior to transition to open-label CZP. However, this dosing approach is justified in all transitioning subjects as there will be no change in benefit-risk due to administration of loading dose and the blinding will be maintained in the study, preserving the data integrity.

Has been changed to:

In accordance with prescribing information for CZP, 3 loading doses of 400mg Q2W should be administered upon initiation of therapy. Thus all subjects who withdraw from double-blind treatment prior to Week 52 and transition to open-label CZP within the AS0006 study will receive this loading dose prior to the maintenance dose of 200mg Q2W. It is recognized that some subjects would have been on active CZP prior to transition to open-label CZP. However, this dosing approach is justified in all transitioning subjects as there will be no change in benefit-risk due to administration of loading dose and the blinding will be maintained in the study, preserving the data integrity.

Change #16

Section 6.3 Withdrawal criteria

Criterion 4:

4. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.

Has been changed to:

4. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test (see Section 12.1.6 for more information regarding pregnancies).

Change #17

A new subsection has been added:

Section 6.4 Eligibility for the SFE Period

To be eligible to participate in the SFE Period, subjects on double-blind study treatment and subjects who withdrew from double-blind study treatment and transitioned to open-label CZP treatment must complete all of the Week 52 visit assessments. Subjects on alternative treatments are not eligible to participate in the SFE Period.

Eligible subjects are allowed to roll-over to the SFE-Period up to 3 months after completion of the Week 52 assessments.

Prior to initiating the SFE assessments, all subjects will be asked to read and sign a separate informed consent form.

Questions concerning the eligibility of a subject to continue participation in the study should be made in consultation with the Medical Monitor.

Change #18

Section 7.2.1 Treatment administration

Paragraph 1, first sentence:

A pharmacy manual will be provided to each site containing instructions regarding drug preparation and dosing. The injection schedule is described in Section 7.2.2.

Has been changed to:

A pharmacy manual will be provided to each site containing instructions regarding drug preparation and dosing. The injection schedule through Week 52 is presented in Figure 7–1. The injection schedule for the SFE Period is presented in Figure 7–2.

And new paragraphs 4, 5, and 6 were added

During the SFE Period, CZP will be administered sc by dedicated unblinded study personnel at the study site on Weeks 52, 54, and 56 for subjects completing double-blind treatment in order to maintain the blind. Subjects who complete the Week 52 visit on placebo treatment will receive loading doses of CZP 400mg at these visits. Subjects who complete the Week 52 visit on CZP treatment will receive 1 injection of CZP 200mg and 1 injection of placebo at these visits to continue their previous CZP treatment regimen.

Subjects who withdrew from double-blind study treatment and transitioned to open-label CZP treatment do not need to visit the site at Week 54 and Week 56, and should continue their open-label CZP treatment regimen.

For the remainder of the SFE Period, CZP can be administered at the site by dedicated study personnel, or by self-injection of the subject under the supervision of the dedicated study personnel, or subjects may self-administer their study treatment Q2W at home.

Change #19

The title of the figure:

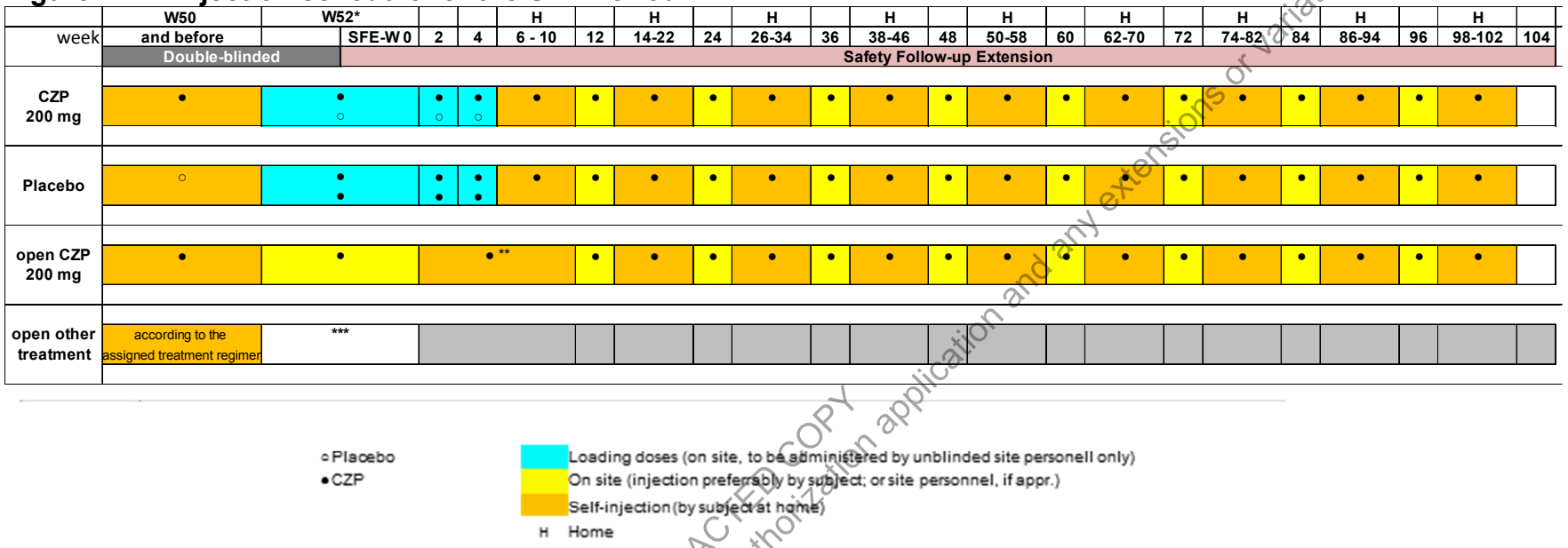
Figure 7-1: Injection schedule

Has been changed to:

Figure 7-1: Injection schedule through Week 52

Change #20An injection schedule for the OLE Period (Figure 7-2) has been added:

Figure 7–2: Injection schedule for the SFE Period



CZP=Certolizumab pegol; FU=follow-up; H=home; SFE=Safety Follow-Up Extension; W=week

* Subjects who complete either double-blind treatment or open-label CZP-treatment and all assessments at Week 52 are eligible to roll-over to the SFE Period. Subjects who complete alternative treatment must finish the study at Week 52 and be scheduled for the final FU visit (8 weeks after the Week 52 visit).

** Subjects rolling over from open-label CZP-treatment to the SFE Period can self-administer their study medication at home from Weeks 2 to 10.

*** Subjects will complete the study assessments at Week 52 according to the protocol and be invited for the final FU visit 8 weeks after Week 52.

Change # 21

Section 7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language. Details on Labeling will be provided in the Pharmacy manual.

Has been changed to:

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language. Details on Labeling will be provided in the Pharmacy manual.

Change #22

7.8.1 Permitted concomitant treatments for axSpA (medications and therapies)

Paragraph 12

If the Investigator discontinues the double-blind study treatment and initiates therapy with CZP, UCB will supply the subject with the CZP. UCB is offering CZP in accordance with the local regulatory requirements for a maximum duration of 2 years or until marketing authorization is granted for CZP (if applicable), whichever comes first. If the decision is made to start a different treatment (including biologics), UCB will not be supplying the medication.

Has been changed to:

If the Investigator discontinues the double-blind study treatment and initiates therapy with CZP, UCB will supply the subject with the CZP. If the decision is made to start a different treatment (including biologics), UCB will not be supplying the medication.

Change #23

A new subsection has been added:

Section 7.8.3 Concomitant medication(s)/treatments during the SFE Period

At the completion of the Week 52 visit assessments, subjects on double-blind study treatment may receive open-label CZP treatment for an additional 2 years (SFE Period). During this time, CZP will be provided by the Sponsor. Concomitant medication usage during the SFE Period is at the discretion of the Investigator.

Change #24

Section 7.9 Blinding

Paragraph 1, first sentence:

Due to differences in presentation and viscosity between CZP and placebo, special precautions will be taken in order to ensure blinding of the study.

Has been changed to:

Due to differences in presentation and viscosity between CZP and placebo, special precautions will be taken in order to ensure blinding during the Double-Blind Period of the study.

Change #25

Section 7.9.1 Maintenance of study treatment blind

A 4th paragraph has been added:

For the SFE Period, in order to maintain the blind for subjects completing the Double-Blind Period, study treatment will be administered sc by unblinded study staff at the study site on Weeks 52, 54, and 56. Subjects who completed the Week 52 visit on placebo treatment will receive loading doses of CZP 400mg at these visits. Subjects who completed the Week 52 visit on CZP treatment will receive 1 injection of CZP 200mg and 1 injection of placebo at these visits to continue their previous CZP treatment regimen.

Change #26

Section 7.10.2 Randomization

The following sentence

The IXRS will be designed to ensure that at least 20% and no more than 40% of the randomized subjects belong to 1 of the 3 clinical subgroups above.

Has been changed to:

The IXRS will be designed to ensure that at least 20% of the randomized subjects belong to each of the 3 clinical subgroups above.

Change #27

Section 8 Study procedures by visit

Paragraphs 2 and 3:

During the study the Investigator will assess the subjects over the entire study period of approximately 66 weeks including a FU Period of 8 weeks after the final Week 52/WD visit.

Visit windows of ±3 days on either side of the scheduled visit are permitted; however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±3 days is relative to Baseline and is applicable for all subsequent visits. Changes to the dosing schedule outside of the 3-day window must be discussed with the Medical Monitor and may result in subject withdrawal.

Has been changed to:

During the first 3 periods of the study the Investigator will assess the subjects over the entire study period of approximately 66 weeks including a FU Period of 8 weeks after the Week 52/WD visit. Visit windows of ±3 days on either side of the scheduled visit are permitted; however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±3 days is relative to Baseline and is applicable for all subsequent visits. Changes to the dosing schedule outside of the 3-day window must be discussed with the Medical Monitor and may result in subject withdrawal.

Change #28

Section 8.5 Week 52/WD (±3 days)

The last bullet:

- Contact IXRS to indicate that subject has completed or withdrawn from the study

Has been changed to:

- Contact IXRS to indicate that subject has rolled over to the SFE Period or withdrawn from the study

Change #29

A new subsection 8.6 has been added and subsequent subsections were renumbered accordingly:

Section 8.6 SFE Period (Week 52 to Week 156)

All eligible subjects must complete the Week 52 visit assessments.

Eligible subjects are allowed to roll-over to the SFE-Period up to 3 months after completion of the Week 52 assessments.

Prior to rolling over to the SFE Period, subjects will be asked to read and sign a separate informed consent form.

Telephone contacts are upon the discretion of the Investigator. Starting at Week 56, and at the discretion of the Investigator, it is recommended to contact the subject by phone at least once in between the on-site visits.

Starting at Week 64, all subjects are to visit the site approximately every 12 weeks for assessments performed according to local standard medical practice, as needed, including:

- Document AEs (Note: any [possible] drug-related AE must be followed-up, at least by phone.)
- Contact IXRS
  - to register the visit and obtain next kit number at Weeks 54 and 56 for subjects receiving loading doses of study drug administration at the study site
  - to register the visit and obtain next kit number for subjects receiving study drug administration at the study site approximately Q12W during the remainder of the study
  - to indicate that subject has completed the SFE Period or withdrawn from the study (Week156/WD)

Change #30

Section 8.6 FU visit (8 weeks after the Week 52/WD visit [±3 days])

Has been renumbered section 8.7 and a new paragraph has been added:

Subjects not participating in the SFE Period will attend a FU visit 8 weeks after the Week 52/WD visit (±3 days).

Change #31

Section 12.1.6 Pregnancy

Paragraph 1:

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately notify UCB's Drug Safety (DS) department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as the pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an Early Withdrawal Visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the Early Withdrawal Visit.
- A FU visit should be scheduled 8 weeks after the Week 52/WD visit.

Has been changed to:

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately notify UCB's Drug Safety (DS) department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as the pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an Early Withdrawal Visit.
- The subject should immediately stop the intake of the IMP.
- A FU visit should be scheduled 8 weeks after the Week 52/WD visit.

And the following paragraph has been added:

Should a subject become pregnant while participating in the study, the subject may be offered the option to enroll in a separate observational pregnancy follow-up study sponsored by UCB and conducted independently from study AS0006. If the study is available locally, the AS0006 Principle Investigator will be provided with the locally approved information about the observational pregnancy follow-up study to inform the subject at the time the pregnancy is reported. Participation in this separate study will be voluntary and will not impact therapeutic management of the subject nor interfere with termination and follow-up procedures as described in study protocol AS0006.

Change #32

Section 12.3 Adverse events of interest

A new paragraph 2 has been added:

Note : Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of interest (ie, without waiting for

any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

Change #33

Section 12.5 Laboratory measurements

The title of Table 12–1: Laboratory measurements

Have been changed to:

Table 12–1 Laboratory measurements up to Week 52 (including the FU visit (8 weeks after the Week 52/WD visit)

And new paragraph 3 has been added beneath the table:

For subjects participating in the SFE Period after Week 52, it is recommended that laboratory assessments be performed at the local laboratory at the discretion of the Investigator according to local standard medical practice to evaluate potential AEs.

Change #34

Section 12.6.1 Pregnancy testing

A new paragraph 2 has been added:

For subjects participating in the SFE Period after Week 52, it is recommended that pregnancy testing be performed according to local standard medical practice.

Change #35

Section 12.6.2 Physical assessments

Paragraph 1:

Physical examination will be performed at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 24, 36, 52/WD, and at the FU visit (8 weeks after the Week 52/WD visit). Physical examination findings will be recorded in the CRF only at Screening. Clinically important abnormal changes in subsequent physical examinations will be recorded as AEs. Physical examinations must be documented in source documentation.

Have been changed to:

Physical examination will be performed at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 24, 36, 52/WD, and at the FU visit (8 weeks after the Week 52/WD visit for subjects not participating in the SFE Period). It is recommended that physical examinations be performed according to local standard medical practice for subjects participating in the SFE Period after Week 52,

And paragraph 4:

In addition the TB signs and symptoms will be assessed at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 24, 36, completion at Week 52/WD visit and FU (8 weeks after the Week 52/WD visit).

Has been changed to:

In addition, the TB signs and symptoms will be assessed at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 24, 36, completion at Week 52/WD visit and FU (8 weeks after the Week 52/WD visit for subjects not participating in the SFE Period).

Change #36

Section 12.6.3 Assessment and management of TB and TB risk factors

Paragraphs 10-13:

Active TB/NTMB

Subjects who develop active TB or NTMB infection during the study (conversion demonstrated by IGRA) must be immediately discontinued from study medication, and a withdrawal visit must be scheduled as soon as possible, but not later than the next regular visit. The subject should be encouraged to keep the FU visit (8 weeks after the Week 52/WD visit). The TB must be documented as an SAE. Treatment for TB should be started based on local guidelines.

Note that subjects with history of or active NTMB infection are excluded from the study regardless of prior or current therapy.

Confirmed active TB is an SAE and an adverse event of special interest (AESI) and must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirement until such time as the TB infection resolves.

Subjects who prematurely discontinue treatment for LTB, or, in the opinion of the Investigator or Sponsor, are noncompliant with anti-TB therapy must discontinue further use of study medication and be immediately withdrawn. Once withdrawn from study treatment, subjects should return for the Week 52/WD visit, complete all Week 52/WD assessments, and complete a FU visit (8 weeks after the Week 52/WD visit).

Have been changed to:

Active TB/NTMB

Subjects who develop active TB or NTMB infection during the study (conversion demonstrated by IGRA) must be immediately discontinued from study medication, and a withdrawal visit must be scheduled as soon as possible, but not later than the next regular visit. The subject should be encouraged to keep the FU visit (8 weeks after the Week 52/WD visit for subjects not participating in the OLE Period). The TB must be documented as an SAE. Treatment for TB should be started based on local guidelines.

Note that subjects with history of or active NTMB infection are excluded from the study regardless of prior or current therapy.

Confirmed active TB is an SAE and an adverse event of special interest (AESI) and must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirement until such time as the TB infection resolves.

Subjects who prematurely discontinue treatment for LTB, or, in the opinion of the Investigator or Sponsor, are noncompliant with anti-TB therapy must discontinue further use of study medication and be immediately withdrawn. Once withdrawn from study treatment, subjects not participating in the OLE Period should return for the Week 52/WD visit, complete all Week 52/WD assessments, and complete a FU visit (8 weeks after the Week 52/WD visit).

Change #37

Section 12.6.3.1 Tuberculosis assessments

Paragraph 1, first sentence:

During conduct of the study the TB assessment by IGRA will be performed at Screening and should be repeated at Week 52/WD for all subjects.

Has been changed to:

During conduct of the study the TB assessment by IGRA will be performed at Screening and should be repeated at Week 52/WD for all subjects not participating in the SFE Period. It is recommended that TB testing be performed according to local standard medical practice during the SFE Period.

Change #38

Section 12.6.3.2 Chest x-ray

Paragraph 1:

A plain posteroanterior chest x-ray must be done at Screening unless a chest x-ray (or a computed tomography of the chest) has been done within 3 months prior to the Screening visit. The chest x-ray must be clear of signs of TB infection (previous or current) before first study drug administration. The chest x-ray will be repeated at Week 52/WD visit (if chest x-ray was performed more than 12 weeks prior to Week 52/WD visit), only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

Has been changed to:

A plain posteroanterior chest x-ray must be done at Screening unless a chest x-ray (or a computed tomography of the chest) has been done within 3 months prior to the Screening visit. The chest x-ray must be clear of signs of TB infection (previous or current) before first study drug administration. For subjects not participating in the SFE Period the chest x-ray will be repeated at Week 52/WD visit (if chest x-ray was performed more than 12 weeks prior to Week 52/WD visit), only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). It is recommended that the chest x-ray be repeated for subjects participating in the SFE Period, if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe

infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

Change #39

Section 12.6.3.3 QuantiFERON or Elispot testing

At Screening all subjects will have an IGRA test (QuantiFERON tube test or Elispot, if QuantiFERON test indicated is not available). The TB test will be repeated at completion at Week 52/WD. Results of the tests will be reported as positive, negative, or indeterminate.

Has been changed to:

At Screening all subjects will have an IGRA test (QuantiFERON tube test or Elispot, if QuantiFERON test indicated is not available). The TB test will be repeated at completion at Week 52/WD for subjects not participating in the SFE Period. It is recommended that TB testing be performed according to local standard medical practice during the SFE Period. Results of the tests will be reported as positive, negative, or indeterminate.

Change #40

Section 12.6.4 Vital signs

Paragraph 2:

Vital signs, including temperature will be measured at all on-site visits including the FU visit (8 weeks after the Week 52/WD visit) with the exception of the Week 1 visit (respiration rate will be measured at Screening and Baseline only unless the subject has an AE).

Has been changed to:

Vital signs, including temperature will be measured at all on-site visits including the FU visit (8 weeks after the Week 52/WD visit) with the exception of the Week 1 visit (respiration rate will be measured at Screening and Baseline only unless the subject has an AE). It is recommended that vital signs be measured according to local standard medical practice during the SFE Period.

Change #41

Section 14.1 Definition of analysis sets

A new paragraph 6 was added:

The SFE Safety Set (SFE-SS) will be defined as all subjects who continued into the SFE Period and who received at least 1 dose of CZP in the SFE Period.

Change #42

Section 14.5 Other efficacy analyses

Paragraph 1, first sentence:

Treatment group comparisons for CZP 200mg Q2W versus placebo will be performed based on the change from Baseline in other selected efficacy variables.

Has been changed to:

Double-Blind Period treatment group comparisons for CZP 200mg Q2W versus placebo will be performed based on the change from Baseline in other selected efficacy variables.

Change #43

Section 14.6 Planned safety and other analyses

The following text was added:

The Safety Set (SS) will be used for analysis of safety data from the Double-Blind Period as well as the combined Double-Blind and SFE Period (as applicable), and the SFE-SS will be used for analysis of safety data from the SFE Period.

Change #44

Section 14.9 Planned interim analysis and data monitoring

A new paragraph 1 was added:

An interim analysis is planned after the completion of the Double-Blind Period of the last subject at Week 52. At this time, the database from the Double-Blind Period will be locked, the treatment codes will be made available to relevant UCB personnel, and an interim study report will be written. The Investigators and subjects will remain blind to the assigned CZP dose regimen of the Double-Blind Period. After the completion of the SFE Period of the last subject, the database will be locked, and a final study report will be written. From the Week 52 Visit onward, subjects will be treated with open-label CZP until the last dosing visit of the study (SFE Week 104).

18.16 Protocol Amendment 4

Rationale for the amendment

The purpose of this substantial amendment is to add an alternative primary efficacy variable for Canada and any other country where applicable or where requested by Regulatory Authorities. In response to feedback from the Canadian Health Authorities, the primary efficacy variable for Canada (and any other country where applicable or where requested by Regulatory Authorities) will be the ASAS40 response at Week 12. For these geographies, the ASDAS-MI at Week 52 was moved to the list of secondary efficacy variables. In addition, the following 3 efficacy variables have been added to the bottom of the testing hierarchy lists for all countries:

- Change from Baseline in ASQoL at Week 52 (elevated from "other" to "secondary" efficacy variable)
- Change from Baseline in nocturnal spinal pain [NRS] at Week 52 (elevated from "other" to "secondary" efficacy variable)
- Number of subjects with AU or new AU flares through Week 52 (new variable)

Specific changes to the lists of efficacy variables, the hierarchical testing procedure, and statistical analyses are described in detail below.

Other changes in this amendment include replacement of the current assay for measuring anti-CZP (anti-drug antibodies) in plasma samples (a validated screening enzyme-linked immunosorbent assay (ELISA) method based on a double-antigen sandwich [bridge] format) with new methods in order to align with current regulatory guidelines. This change is being made across the CZP development program. In the current version of the AS0006 protocol, an ADAb level >2.4 units/mL is defined as positive according to the bioanalytical method and testing strategy. The updated strategy for immunogenicity testing will take a tiered approach consisting of initial screening for ADAb positive samples in subjects randomized to CZP or placebo, using a population-specific cutpoint resulting in a 5% false positive rate. Samples scored positively in the screening assay will be confirmed using a confirmatory assay with a population-specific confirmatory cutpoint resulting in a 1% false positive rate. Characterization of confirmed positive samples will consist of determination of the titer, and for a subset of samples, assessment of the neutralizing potential using a cell-based neutralizing antibody assay.

An additional change to the amendment is to correctly describe the version of the MOS Sleep Scale used in the study. References to the older 6-point scale, which was not used, were updated to reflect the newer 5-point scale, and a copy of the 6-point scale questionnaire in Appendix 18.8 was replaced with the correct 5-point scale questionnaire.

Additional minor changes to the protocol include correction of the order of presentation of the subsections for secondary and other efficacy variables, and corrections of minor typographical errors. Specific changes are listed below.

Modifications and changes

Specific changes

Change #1

Section 1 Summary

Paragraph 13:

The primary efficacy variable is Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) response at Week 52. The secondary efficacy variables are ASAS 40% (ASAS40) response at Weeks 12 and 52, change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Weeks 12 and 52, change from Baseline in BASDAI at Weeks 12 and 52, change from Baseline in SI joint Spondyloarthritis Research Consortium of Canada (SPARCC) score at Week 12, and the number of subjects without relevant changes to background medication.

Has been changed to:

The primary efficacy variable is Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) response at Week 52. The secondary efficacy variables are ASAS 40% (ASAS40) response at Weeks 12 and 52, change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Weeks 12 and 52, change from Baseline in BASDAI at Weeks 12 and 52, change from Baseline in SI joint Spondyloarthritis Research Consortium of Canada (SPARCC) score at Week 12, the number of subjects without relevant changes to background medication, change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) at Week 52, change from Baseline in nocturnal spinal pain (NRS) at Week 52, and the number of subjects with anterior uveitis (AU) or new AU flares through Week 52.

And a new paragraph 14 has been added:

For Canada (and any other country where applicable or where requested by Regulatory Authorities), the primary efficacy variable is the ASAS40 response at Week 12. The secondary efficacy variables are ASAS40 response at Week 52, ASDAS-MI at Week 52, change from Baseline in BASFI at Weeks 12 and 52, change from Baseline in BASDAI at Weeks 12 and 52, change from Baseline in SI joint SPARCC score at Week 12, the number of subjects without relevant changes to background medication, change from Baseline in ASQoL at Week 52, change from Baseline in nocturnal spinal pain (NRS) at Week 52, and the number of subjects with AU or new AU flares through Week 52.

Change #2

Section 3.3 Other objectives

The other objectives of the study are to assess the effect of CZP on the following:

- Spinal mobility
- Total and nocturnal spinal pain (NRS)

Has been changed to:

The other objectives of the study are to assess the effect of CZP on the following:

- Spinal mobility
- Total spinal pain (NRS)

Change #3

Section 4.1.1 Primary efficacy variable

- ASDAS-MI at Week 52

Has been changed to:

- ASDAS-MI at Week 52

The primary efficacy variable for Canada (and any other country where applicable or where requested by Regulatory Authorities) is the ASAS40 response at Week 12.

Change #4

The subsection for "other efficacy variables" was moved down and the header was corrected from Section 4.1.2 to Section 4.1.3.

Section 4.1.3 Other efficacy variables

And the following variables were removed from the list of other efficacy variables:

- Nocturnal spinal pain (NRS)
- Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL)

Change #5

The subsection for "secondary efficacy variables" was moved up and the header was corrected from Section 4.1.3 to Section 4.1.2.

Section 4.1.2 Secondary efficacy variables

And the following variables were added to the list of secondary efficacy variables:

- Change from Baseline in ASQoL at Week 52
- Change from Baseline in ASQoL at timepoints other than Week 52
- Change from Baseline in nocturnal spinal pain (NRS) at Week 52
- Number of subjects with AU or new AU flares through Week 52

And a new paragraph has been added:

For Canada (and any other country where applicable or where requested by Regulatory Authorities), the secondary efficacy variables are:

- ASAS40 response at Week 52
- ASDAS-MI at Week 52
- Change from Baseline in BASFI at Weeks 12 and 52

- Change from Baseline in BASDAI at Weeks 12 and 52
- Change from Baseline in SI joint SPARCC score at Week 12
- Number of subjects without relevant changes to background medication
- Change from Baseline in ASQoL at Week 52
- Change from Baseline in ASQoL at timepoints other than Week 52
- Change from Baseline in nocturnal spinal pain (NRS) at Week 52
- Number of subjects with AU or new AU flares through Week 52

Change #6

Section 4.3 Immunological variables

Anti-CZP antibody (anti-CZP Ab) concentrations will be assessed at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52/WD, and the FU visit (8 weeks after the Week 52/WD visit). In addition, the anti-CZP Ab concentrations will be assessed in subjects who withdraw from study drug and transition to open-label CZP.

The number and percent of subjects with anti-CZP Ab concentrations above 2.4 units/mL will be reported as follows:

- Number and percentage of subjects with anti-CZP Ab >2.4 units/mL at the time of each visit
- Number and percentage of subjects with anti-CZP Ab >2.4 units/mL at any visit during treatment (not including posttreatment withdrawal or FU visits)
- Number and percentage of subjects with anti-CZP Ab >2.4 units/mL at any visit including posttreatment withdrawal or FU visits

Has been changed to:

Anti-CZP antibody/anti-drug antibody (anti-CZP Ab/ADAb) concentrations will be assessed at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52/WD, and the FU visit (8 weeks after the Week 52/WD visit). In addition, the anti-CZP Ab concentrations will be assessed in subjects who withdraw from study drug and transition to open-label CZP.

Determination of ADAb will be done using a validated screening, confirmation and titration ADAb bridging assay, with potential further characterization by a neutralizing antibody assay. The immunogenicity data will be processed according to dedicated Bioanalytical Analysis plans.

Change #7

Section 9.1.11 MOS Sleep Scale

Paragraph 2, second sentence:

The frequency with which each problem has been experienced during the previous 4 weeks is rated on a 6-point scale ranging from “none of the time” to “all of the time,” except sleep quantity, which is reported in hours.

Has been changed to:

The frequency with which each problem has been experienced during the previous 4 weeks is rated on a 5-point scale ranging from "none of the time" to "all of the time," except sleep quantity, which is reported in hours.

Change #8

Section 10 Assessment of pharmacokinetics, exploratory biomarkers, and pharmacogenomics variables

Paragraph 2

These plasma samples may be used for possible analyses of exploratory biomarkers, selected from the following list: MMP-3, BMP-2, -4 and -7, WNT1, WISP, Gremlin, DKK1, Sclerostin, Hedgehog proteins (Shh, Ihh, Dhh), Collagen turnover/cleavage products, collagen type X, VEGF, citrullinated vimentin fragments, cytokines: IL13, IL17 A and F, IL23, IL34, (TGF-β, M-CSF, GM-CSF, CSF-1, sCSF1r levels. The results of the analyses of CZP and its constituent moieties from alternative methods may be reported separately.

Has been changed to:

These plasma samples may be used for possible analyses of exploratory biomarkers which might include, but are not limited to: MMP-3, BMP-2, -4 and -7, WNT1, WISP, Gremlin, DKK1, Sclerostin, Hedgehog proteins (Shh, Ihh, Dhh), Collagen turnover/cleavage products, collagen type X, VEGF, citrullinated vimentin fragments, cytokines: IL13, IL17 A and F, IL23, IL34, (TGF-β, M-CSF, GM-CSF, CSF-1, sCSF1r levels. The results of the analyses of CZP and its constituent moieties from alternative methods may be reported separately.

Change #9

Section 11 ASSESSMENT OF IMMUNOGENICITY VARIABLES

Plasma samples for the measurement of anti-CZP antibodies will be taken at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52/WD, and the FU visit (8 weeks after the Week 52/WD visit).

The number and percent of subjects with anti-CZP concentrations above 2.4 units/mL will be reported as follows:

- At the time of each visit
- At any visit during treatment (not including posttreatment withdrawal or FU visits)
- At any visit including posttreatment withdrawal or FU visits

The sampling, handling, and shipment of samples will be performed as detailed in the Laboratory Manual.

Has been changed to:

Plasma samples for the measurement of anti-CZP antibodies and potentially neutralizing antibodies will be taken at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52/WD, and the FU visit (8 weeks after the Week 52/WD visit).

The sampling, handling, and shipment of samples will be performed as detailed in the Laboratory Manual.

Change #10

Section 14.1 Definition of analysis sets

Paragraph 4:

The Full Analysis Set (FAS) will consist of all subjects in the RS who have received at least 1 dose of study medication and who have a valid Baseline efficacy measurement for ASDAS.

Has been changed to:

The Full Analysis Set (FAS) will consist of all subjects in the RS who have received at least 1 dose of study medication.

Change #11

Section 14.2 General statistical considerations

All efficacy analyses will be performed using the FAS. The PPS will be used for a sensitivity analysis on the primary endpoint only.

The statistical analysis of the primary efficacy variable and selected secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure. The predefined order of hypothesis testing, each at a 2-sided 0.05 significance level for the comparison between CZP 200mg Q2W and placebo, will be performed in the sequence shown below. After the first test, each subsequent test is performed only if the previous test is significant in favor of CZP at the 2-sided 0.05 level. Note that the first test relates to the primary efficacy variable while the others provide the sequence testing for selected secondary efficacy variables.

1. ASDAS-MI response at Week 52
2. ASAS40 response at Week 12
3. Change from Baseline in BASDAI at Week 12
4. Change from Baseline in BASFI at Week 12
5. ASAS40 response at Week 52
6. Change from Baseline in BASDAI at Week 52
7. Change from Baseline in BASFI at Week 52
8. Change from Baseline in SI joint SPARCC score at Week 12

Variables evaluated over time will be summarized using imputed and observed case values. Further details on data summarization will be provided in the SAP.

Has been changed to:

All efficacy analyses will be performed using the FAS. The PPS will be used for a sensitivity analysis on the primary endpoint only.

The statistical analysis of the primary efficacy variable and selected secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure. The predefined order of hypothesis testing, each at a 2-sided 0.05 significance level for the comparison between CZP 200mg Q2W and placebo, will be performed in the sequence shown below. After the first test, each subsequent test is performed only if the previous test is significant in favor of CZP at

the 2-sided 0.05 level. Note that the first test relates to the primary efficacy variable while the others provide the sequence testing for selected secondary efficacy variables.

1. ASDAS-MI response at Week 52
2. ASAS40 response at Week 12
3. Change from Baseline in BASDAI at Week 12
4. Change from Baseline in BASFI at Week 12
5. ASAS40 response at Week 52
6. Change from Baseline in BASDAI at Week 52
7. Change from Baseline in BASFI at Week 52
8. Change from Baseline in SI joint SPARCC score at Week 12
9. Change from Baseline in ASQoL at Week 52
10. Change from Baseline in nocturnal spinal pain (NRS) at Week 52
11. Number of subjects with AU or new AU flares through Week 52

Hierarchical testing of efficacy variables for Canada and any other country where applicable:

1. ASAS40 response at Week 12
2. ASDAS-MI response at Week 52
3. Change from Baseline in BASDAI at Week 12
4. Change from Baseline in BASFI at Week 12
5. ASAS40 response at Week 52
6. Change from Baseline in BASDAI at Week 52
7. Change from Baseline in BASFI at Week 52
8. Change from Baseline in SI joint SPARCC score at Week 12
9. Change from Baseline in ASQoL at Week 52
10. Change from Baseline in nocturnal spinal pain (NRS) at Week 52
11. Number of subjects with AU or new AU flares through Week 52

Variables evaluated over time will be summarized using imputed and observed case values. Further details on data summarization will be provided in the SAP.

Change #12

Section 14.3 Planned efficacy analyses

A new paragraph 4 has been added

For Canada (and any other country where applicable or where requested by Regulatory Authorities), the primary efficacy variable measurement is the ASAS40 response at Week 12.

Analysis of the ASAS40 response at Week 12 will be performed as described above for ASDAS-MI response at Week 52. Similar to the ASADAS-MI efficacy endpoint, the ASAS40 will be treated as a composite endpoint when it is analyzed. Specifically, subjects will need to: 1) achieve the relevant response (ASAS40); and 2) remain in the study and on their randomized double-blind study treatment through Week 12.

Paragraph 5 has been revised:

Subgroup analyses by age, gender, race, symptom duration, smoking history, HLA-B27 genotype, anti-CZP Ab status, region, prior anti-TNF exposure, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) will be performed for the primary efficacy variable. Subgroup analyses will be summarized using descriptive statistics only.

Has been changed to:

Subgroup analyses by age, gender, race, symptom duration, smoking history, HLA-B27 genotype, anti-CZP Ab (ADAb) status, region, prior anti-TNF exposure, Baseline SPARCC score ≥5, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) will be performed for the primary efficacy variable. Subgroup analyses will be summarized using descriptive statistics only.

Change #13

Section 14.4 Secondary efficacy analyses

The changes from Baseline in BASDAI and BASFI at Week 12 and Week 52 are specified as secondary efficacy variables. As these are continuous variables, missing data must be handled using a different approach from what is specified for the primary efficacy endpoint (a responder variable). In the current study, Investigators will be given discretion to discontinue the double-blind study treatment for subjects not responding in order to provide them with alternative therapy to treat the condition. Therefore, in many cases, missing efficacy data due to the double-blind study treatment discontinuation should be dependent on the observed efficacy scores, but independent of unobserved data. This would be consistent with a missing at random (MAR) assumption. However, the possibility of discontinuation due to tolerability or other unobserved data cannot be completely discounted. Therefore, a missing not at random mechanism will be used for the analysis of continuous secondary efficacy variables.

A reference-based multiple imputation (MI) procedure will be used for this analysis, which will impute missing data as well as data at the time points following the discontinuation of the double-blind study treatment for both the CZP and placebo groups. This procedure will use an imputation model developed based on available data from the placebo group, thereby assuming a placebo trajectory for missing data following study treatment discontinuation for subjects in both treatment groups (Mallinckrodt, 2013). The estimand being evaluated in this case is the difference in the outcome of improvement in all randomized subjects at the planned endpoint, attributable to the initially randomized medication. This is an effectiveness estimand of the de facto hypothesis which has been referred to as “estimand 6” (Mallinckrodt, 2012).

Additionally, change from Baseline in SI joint SPARCC score at Week 12 is a continuous secondary efficacy variable. The same MI procedure specified as the main analysis approach for BASDAI and BASFI will be used to account for missing SPARCC data. However, it should be noted that, unlike BASDAI and BASFI, SPARCC score will not be measured at any time points

between Baseline and Week 12, meaning that those are the only 2 time points that can be considered in the evaluation of SPARCC score at Week 12. Comparisons between treatment groups will be made using an analysis of covariance (ANCOVA) model on the imputed data set. The model will include Baseline score, treatment group, region, and MRI/CRP classification.

The ASAS40 response at Week 12 and Week 52 are responder secondary efficacy endpoints. As a responder variable, ASAS40 will be analyzed using logistic regression based on a model similar to the one described for the primary analysis. As with the primary efficacy endpoint, the ASAS40 will be treated as a composite endpoint when it is analyzed. Specifically, subjects will need to 1) achieve the relevant response (ASAS40) and 2) remain in the study and on their randomized double-blind study treatment through the time point being analyzed (Week 12 or Week 52).

The comparison of CZP 200mg Q2W to placebo as described above for the ASAS40 response, BASDAI, and BASFI at Week 12 and Week 52 and for SI joint SPARCC score at Week 12 will be part of the fixed sequence testing procedure outlined in Section 14.2.

Additionally, sensitivity analyses will be conducted on these secondary efficacy endpoints. In particular, the assumptions related to missing data will be investigated further. These analyses are described in Section 14.8.

An additional secondary efficacy variable is the number of subjects with relevant changes to background medication. This variable will be based on whether or not subjects take certain pre-specified background medications during the course of the study and will be defined in the SAP. The analysis for this variable will use the same logistic regression model described for the primary variable.

Has been changed to:

The changes from Baseline in BASDAI and BASFI at Week 12 and Week 52, change from Baseline in ASQoL at Week 52, and change from Baseline in nocturnal spinal pain at Week 52are specified as secondary efficacy variables. As these are continuous variables, missing data must be handled using a different approach from what is specified for the primary efficacy endpoint (a responder variable). In the current study, Investigators will be given discretion to discontinue the double-blind study treatment for subjects not responding in order to provide them with alternative therapy to treat the condition. Therefore, in many cases, missing efficacy data due to the double-blind study treatment discontinuation should be dependent on the observed efficacy scores, but independent of unobserved data. This would be consistent with a missing at random (MAR) assumption. However, the possibility of discontinuation due to tolerability or other unobserved data cannot be completely discounted. Therefore, a missing not at random mechanism will be used for the analysis of continuous secondary efficacy variables.

A reference-based multiple imputation (MI) procedure will be used for this analysis, which will impute missing data as well as data at the time points following the discontinuation of the double-blind study treatment for both the CZP and placebo groups. This procedure will use an imputation model developed based on available data from the placebo group, thereby assuming a placebo trajectory for missing data following study treatment discontinuation for subjects in both treatment groups (Mallinckrodt, 2013). The estimand being evaluated in this case is the difference in the outcome of improvement in all randomized subjects at the planned endpoint,

attributable to the initially randomized medication. This is an effectiveness estimand of the de facto hypothesis which has been referred to as “estimand 6” (Mallinckrodt, 2012).

Additionally, change from Baseline in SI joint SPARCC score at Week 12 is a continuous secondary efficacy variable. The same MI procedure specified as the main analysis approach for BASDAI and BASFI will be used to account for missing SPARCC data. However, it should be noted that, unlike BASDAI and BASFI, SPARCC score will not be measured at any time points between Baseline and Week 12, meaning that those are the only 2 time points that can be considered in the evaluation of SPARCC score at Week 12. Comparisons between treatment groups will be made using an analysis of covariance (ANCOVA) model on the imputed data set. The model will include Baseline score, treatment group, region, and MRI/CRP classification.

The ASAS40 response at Week 12 and Week 52 are responder secondary efficacy endpoints. (For Canada and any other country where applicable or where requested by Regulatory Authorities, the ASAS40 response at Week 12 is the primary efficacy variable; the ASAS40 response at Week 52 and the ASDAS-MI response at Week 52 are secondary efficacy variables). As a responder variable, ASAS40 will be analyzed using logistic regression based on a model similar to the one described for the primary analysis.

The number of subjects with new onset post-Baseline AU or new AU flares through Week 52 is a categorical secondary efficacy endpoint for all regions. Subjects with a new event at one or more visits post-Baseline will be classified as having had a flare, subjects without new events at all visits post-Baseline will be classified as not having had a flare. As a dichotomous outcome variable, treatment groups will be compared for differences using logistic regression based on a model similar to the one described for the primary analysis.

The comparison of CZP 200mg Q2W to placebo as described above for the ASAS40 response, BASDAI, and BASFI at Week 12 and Week 52, for SI joint SPARCC score at Week 12, for ASQoL at Week 52, nocturnal pain score at Week 52, and number of subjects with AU or new AU flares through Week 52 will be part of the fixed sequence testing procedure outlined in Section 14.2.

Additionally, sensitivity analyses will be conducted on these secondary efficacy endpoints. In particular, the assumptions related to missing data will be investigated further. These analyses are described in Section 14.8.

An additional secondary efficacy variable is the number of subjects with relevant changes to background medication. This variable will be based on whether or not subjects take certain pre-specified background medications during the course of the study and will be defined in the SAP. The analysis for this variable will use the same logistic regression model described for the primary variable.

Change #14

Section 14.5 Other efficacy analyses

Paragraph 2:

The following variables were removed from the list of other efficacy variables

- Nocturnal spinal pain (NRS)
- Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL)

Change #15

Section 14.6.2 Pharmacokinetic and immunogenicity variable analysis

Certolizumab pegol plasma concentrations will be tabulated and summarized by treatment group (overall and by anti-CZP Ab level - above or below 2.4 units/mL within each treatment group) for each visit at which samples were taken using the geometric mean, geometric coefficient of variation, 95% CIs, arithmetic mean, arithmetic SD, minimum and maximum, geomean plasma concentration time curves with their 95% CI will be plotted overall and by anti-CZP Ab status. Individual plasma concentrations for CZP and anti-CZP levels versus time will be produced on the same graph.

The number and percent of subjects with titer above 2.4 units/mL will be presented for each visit, at any visit during treatment (not including posttreatment withdrawal or FU visits) and at any visit including posttreatment withdrawal or FU visits. For the subjects with at least 1 anti-CZP Ab titer above 2.4 units/mL, the first timepoint of occurrence of the titer above 2.4 units/mL will also be displayed.

In addition, safety and efficacy profiles by anti-CZP Ab level will be investigated.

Has been changed to:

Certolizumab pegol plasma concentrations will be tabulated and summarized by treatment group for each visit at which samples were taken using the geometric mean, geometric coefficient of variation, 95% CIs, arithmetic mean, arithmetic SD, minimum and maximum. Individual plasma concentrations for CZP and anti-CZP levels versus time will be produced on the same graph.

Immunogenicity will be assessed through listing of individual results by subject and summary tables. Immunogenicity data will be correlated with PK and efficacy readout. In addition, immunogenicity will be correlated with possible safety findings.

Change #16

Section 14.8 Handling of dropouts or missing data

For analysis purposes, the primary efficacy variable is defined as a composite endpoint in which it is necessary to achieve ASDAS-MI at Week 52 and to remain on randomized double-blind study treatment through Week 52 in order to be considered a responder (see Section 14.3). Because this composite endpoint definition does not allow for a missing response status, no formal method for handling missing data is needed in the primary efficacy analysis. However, in order to assess the impact of various missing data assumptions on the analysis, additional sensitivity analyses of the primary efficacy variable will be performed as follows:

- Including observed data at Week 52: The observed data at Week 52 will be used and analyzed according to randomized treatment, regardless of whether or not the subject is still on his/her randomized double-blind study treatment at that time. Despite efforts to continue to collect data on all subjects (even if they discontinue the double-blind study treatment), there may still be subjects with missing data at Week 52. Such subjects will be considered as non-responders in accordance with the composite endpoint definition outlined above. The same logistic regression model specified for the primary analysis will be used.
- MI: The Markov Chain Monte Carlo (MCMC) method will be used to impute intermittent missing data. The resulting multiply imputed data sets will be monotone missing and will be

imputed using monotone regression (assuming a MAR pattern). Note that the MI procedure will be done on the continuous ASDAS variable, which will be dichotomized for the logistic regression analysis. Ankylosing Spondylitis Disease Activity Score data collected following the discontinuation of double-blind study treatment will be treated as missing in the original data set for this sensitivity analysis.

- Tipping point analysis: In this analysis, various assumptions will be made about average outcomes among the subsets of subjects who prematurely discontinued double-blind study treatment. Various "delta adjustments" will be made to the assumed responses among missing data in each treatment arm with varying degrees of plausibility (O'Kelly, 2014). The goal of the tipping point analysis is to identify assumptions about the missing data under which the conclusions change, ie, under which there is no longer evidence of a treatment effect. Then, the plausibility of such assumptions would be discussed. Further details of this procedure will be described in the SAP.
- Observed case analysis: This analysis will only include the observed data for subjects still on the original double-blind study treatment. Data collected after the discontinuation of double-blind study treatment and all other missing data will be excluded from the analysis. The same logistic regression model specified for the primary efficacy analysis will be performed.

The sensitivity analyses of the secondary binary efficacy variables (ASAS40 at Weeks 12 and 52) will be as follows:

- Including observed data at Week 52: As described for the primary efficacy variable.
- MI: As described for the primary efficacy variable. Note that as ASAS40 is a composite of 4 different variables, the MI procedure will be performed on each of these components, and the ASAS40 response will be derived based on the multiply imputed datasets.
- Reference-based MI: This procedure will impute missing data as well as data at the time points following the discontinuation of the double-blind study treatment for both the CZP and placebo groups. This procedure will use an imputation model developed based on data from the placebo group (Mallinckrodt, 2013). The estimand being evaluated in this case is the difference in the outcome of improvement in all randomized subjects at the planned endpoint, attributable to the initially randomized medication, which has been referred to as "estimand 6" (Mallinckrodt, 2012).
- Observed case analysis: As described for the primary efficacy variable.

The sensitivity analyses of secondary continuous efficacy variables (the change from Baseline in BASDAI and BASFI at Weeks 12 and 52 and the change from Baseline in the SI joint SPARCC score at Week 12) will be as follows:

- Including observed data at Week 52: As described for the primary efficacy variable.
- MI: As described for the primary efficacy variable.
- Observed case analysis: As described for the primary efficacy variable.
- LOCF

Missing data for the other efficacy variables described in Section 14.5 will be handled as follows:

- With imputation: Non-responder imputation for binary variables and LOCF for continuous variables (as described in Section 14.5)
- Observed case analysis: As described for the primary efficacy variable.

Additionally, algorithms for imputing missing or partial dates for safety evaluations will be detailed in the SAP.

Has been changed to:

For analysis purposes, the primary efficacy variable is defined as a composite endpoint in which it is necessary to achieve ASDAS-MI at Week 52 and to remain on randomized double-blind study treatment through Week 52 in order to be considered a responder (see Section 14.3). Because this composite endpoint definition does not allow for a missing response status, no formal method for handling missing data is needed in the primary efficacy analysis. However, in order to assess the impact of various missing data assumptions on the analysis, additional sensitivity analyses of the primary efficacy variable will be performed as follows:

- Including observed data at Week 52: The observed data at Week 52 will be used and analyzed according to randomized treatment, regardless of whether or not the subject is still on his/her randomized double-blind study treatment at that time. Despite efforts to continue to collect data on all subjects (even if they discontinue the double-blind study treatment), there may still be subjects with missing data at Week 52. Such subjects will be considered as non-responders in accordance with the composite endpoint definition outlined above. The same logistic regression model specified for the primary analysis will be used.
- MI: The Markov Chain Monte Carlo (MCMC) method will be used to impute intermittent missing data. The resulting multiply imputed data sets will be monotone missing and will be imputed using monotone regression (assuming a MAR pattern). Note that the MI procedure will be done on the continuous ASDAS variable, which will be dichotomized for the logistic regression analysis. Ankylosing Spondylitis Disease Activity Score data collected following the discontinuation of double-blind study treatment will be treated as missing in the original data set for this sensitivity analysis.
- Tipping point analysis: In this analysis, various assumptions will be made about average outcomes among the subsets of subjects who prematurely discontinued double-blind study treatment. Various "delta adjustments" will be made to the assumed responses among missing data in each treatment arm with varying degrees of plausibility (O'Kelly, 2014). The goal of the tipping point analysis is to identify assumptions about the missing data under which the conclusions change, ie, under which there is no longer evidence of a treatment effect. Then, the plausibility of such assumptions would be discussed. Further details of this procedure will be described in the SAP.
- Observed case analysis: This analysis will only include the observed data for subjects still on the original double-blind study treatment. Data collected after the discontinuation of double-blind study treatment and all other missing data will be excluded from the analysis. The same logistic regression model specified for the primary efficacy analysis will be performed.

Sensitivity analyses of the primary efficacy variable for Canada (and any other country where applicable or where requested by Regulatory Authorities), ASAS40 response at Week 12, will mirror the approach described above for ASDAS-MI at Week 52.

The sensitivity analyses of the secondary binary efficacy variables (ASAS40 at Week 52) will be as follows:

- Including observed data at Week 52: As described for the primary efficacy variable.
- MI: As described for the primary efficacy variable. Note that as ASAS40 is a composite of 4 different variables, the MI procedure will be performed on each of these components, and the ASAS40 response will be derived based on the multiply imputed datasets.
- Reference-based MI: This procedure will impute missing data as well as data at the time points following the discontinuation of the double-blind study treatment for both the CZP and placebo groups. This procedure will use an imputation model developed based on data from the placebo group (Mallinckrodt, 2013). The estimand being evaluated in this case is the difference in the outcome of improvement in all randomized subjects at the planned endpoint, attributable to the initially randomized medication, which has been referred to as "estimand 6" (Mallinckrodt, 2012).
- Observed case analysis: As described for the primary efficacy variable.

For the secondary efficacy variable "number of subjects with AU or new AU flares through Week 52," missing values should only occur in the unlikely case that a subject does not have any post-Baseline AU assessments performed. Therefore, sensitivity analyses for this variable will focus on analyses adjusting for exposure time at risk such as event rate, incidence rate, and confidence interval.

The sensitivity analyses of secondary continuous efficacy variables (the change from Baseline in BASDAI and BASFI at Weeks 12 and 52, and the change from Baseline in the SI joint SPARCC score at Week 12, change from Baseline in ASQoL at Week 52, and change from Baseline in nocturnal spine pain at Week 52) will be as follows:

- Including observed data at Week 52: As described for the primary efficacy variable.
- MI: As described for the primary efficacy variable.
- Observed case analysis: As described for the primary efficacy variable.
- LOCF

Missing data for the other efficacy variables described in Section 14.5 will be handled as follows:

- With imputation: Non-responder imputation for binary variables and LOCF for continuous variables (as described in Section 14.5)
- Observed case analysis: As described for the primary efficacy variable.

Additionally, algorithms for imputing missing or partial dates for safety evaluations will be detailed in the SAP.

Change #17

Section 14.10 Determination of sample size

A new Paragraph 2 has been added

With Protocol Amendment 4, ASAS40 response at Week 12 was elevated to be the primary efficacy variable for Canada (and any other country where applicable or where requested by Regulatory Authorities); however, the study was fully enrolled at the time of this amendment. The expected responder rates for ASAS40 response at Week 12 are also 40% for CZP and 20% for placebo, which are identical to the assumed response rates cited for ASDAS-MI at Week 52. Therefore, the planned total sample size of 300 would provide 95% power for this variable, as well.

Change #18

Section 18.8 MOS Sleep Scale Questionnaire

The copy of the 6-point scale questionnaire in Appendix 18.8, which was not used in this study, was replaced with the correct 5-point scale questionnaire.

19 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

20 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

AS006 Protocol Amendment 4

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	19-Dec-2017 18:24 GMT+01
[redacted]	Clinical Approval	20-Dec-2017 12:59 GMT+01

STATISTICAL ANALYSIS PLAN

Study: AS0006

Product: Certolizumab pegol

PHASE 3, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO EVALUATE EFFICACY AND SAFETY OF CERTOLIZUMAB PEGOL IN SUBJECTS WITH ACTIVE AXIAL SPONDYLOARTHRITIS (AXSPA) WITHOUT X-RAY EVIDENCE OF ANKYLOSING SPONDYLITIS (AS) AND OBJECTIVE SIGNS OF INFLAMMATION

SAP/Amendment Number	Date
Final SAP	14 Jan 2015

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADaM	analysis data model
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
ASAS	Assessment of SpondyloArthritis International Society
ASAS20, 40	Assessment in Axial Spondyloarthritis International Society 20%, 40% response criteria
AS	ankylosing spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASDAS-CII	Ankylosing Spondylitis Disease Activity Score – Clinically Important Improvement
ASDAS-HD	Ankylosing Spondylitis Disease Activity Score – High Disease activity
ASDAS-ID	Ankylosing Spondylitis Disease Activity Score – Inactive Disease
ASDAS-MD	Ankylosing Spondylitis Disease Activity Score – Moderate Disease
ASDAS-MI	Ankylosing Spondylitis Disease Activity Score – Major Improvement
ASDAS-vHD	Ankylosing Spondylitis Disease Activity Score – very High Disease activity
ASQoL	Ankylosing Spondylitis Quality of Life
ASspiMRI-a	Ankylosing Spondylitis spine MRI scoring system for disease activity
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AxSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASDAI50	Bath Ankylosing Spondylitis Disease Activity Index 50% response criteria
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMI	body mass index
BMP	bone morphogenic protein
BP	bodily pain
CI	confidence interval

CK	creatinine kinase
CR	compliance ratio
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
CV	coefficient of variation
CZP	certolizumab pegol
DKK1	dickkopf-related protein 1
DRL	Drug Reference List
DMARD	disease-modifying antirheumatic drug
EAIR	Exposure-adjusted incidence rate
EAER	exposure-adjusted event rate
EQ-5D	EuroQoL Health Status Questionnaire (5 dimensions)
ER	emergency room
ES	Enrolled Set
FAS	Full Analysis Set
GH	general health
HCQ	hydroxychloroquine
HLA-B27	human leukocyte antigen B27
HLT	High Level Term
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation
IVRS	interactive voice response system
LOCF	last observation carried forward
LLN	lower limit of normal
LLOQ	lower limit of quantification
LLT	Low Level Term
MASES	Maastricht Ankylosis Spondylitis Enthesitis Score
MCS	Mental Component Summary
MedDRA®	Medical Dictionary of Regulatory Activities®
MH	mental health
MMP	matrix metalloproteinase
MMRM	mixed effects model for repeated measurements
mNY	Modified New York (criteria)
MOS	Medical Outcomes Study
MRI	magnetic resonance imaging

MTX	methotrexate
NRS	Numeric Rating Scale
NRI	non-response imputation
NSAID	nonsteroidal anti-inflammatory drug
OC	observed case
PBO	placebo
PCS	Physical Component Summary
PF	physical Function
PGADA	Patient's Global Assessment of Disease Activity
PhGADA	Physician's Global Assessment of Disease Activity
PPS	Per Protocol Set
PT	Preferred Term
Q	question
Q1	1st Quartile
Q3	3rd Quartile
Q2W	every 2 weeks (every other week)
QoL	quality of life
RBC	red blood cell
RCTC	Rheumatology Common Toxicity Criteria
RE	role emotional
RP	role physical
RS	Randomized Set
SAARD	slow-acting anti-rheumatic drug
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SD	standard deviation
SDTM	study data tabulation model
SE	standard error
SF	social functioning
SF-36	Short-Form 36-Item Health Survey
SFU	safety follow-up
SI	sacroiliac
SLPQRAW	Sleep Quantity Raw Score
SLPOP1	Optimal Sleep
SM	spinal mobility
SOC	System Organ Class

SOP	standard operating procedure
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
sqrt	square root
SS	Safety Set
SSZ	sulfasalazine
STIR	short-tau-inversion recovery
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
USA	United States of America
ULN	upper limit of normal
VAS	visual analog scale
VT	vitality
VU	vertebral units
WBC	white blood cell
WHO	World Health Organization
WPS	Work Productivity Survey

1 INTRODUCTION

This SAP describes the analysis of the double-blind 52-week treatment period and the 10-week safety follow-up (SFU) period of the AS0006 study. It is designed to support a Clinical Study Report (CSR), is compliant with International Conference on Harmonization (ICH) guidelines and is based on the protocol dated 14 Jan 2015.

2 PROTOCOL SUMMARY

AS0006 is a randomized, double-blind, parallel-group, placebo-controlled study, consisting of 52 weeks of treatment with certolizumab pegol (CZP) and a safety follow up (SFU) period for 10 weeks after the last administration of study medication. The study population is subjects with active axial spondyloarthritis (axSpA) with sacroiliitis on magnetic resonance imaging (MRI) or CRP levels indicative of inflammatory disease but without x-ray evidence of ankylosing spondylitis (AS) who have had an inadequate response to, have a contraindication to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Eligible subjects will be allocated to the following study treatments in a 1:1 ratio:

- CZP administered subcutaneously (sc) at the dose of CZP 400mg at Weeks 0, 2, and 4 followed by CZP 200mg Q2W sc (starting at Week 6)
- Placebo

2.1 Study objectives

2.1.1 Primary objective

The primary objective of the study is to demonstrate the efficacy of CZP 200mg Q2W on the signs and symptoms of subjects with active axSpA without x-ray evidence of ankylosing spondylitis.

2.1.2 Secondary objectives

The secondary objectives of the study are to assess efficacy, safety, and tolerability and to demonstrate the effect of CZP on:

- Health outcomes
- Disease activity
- SI joint inflammation
- Changes to concomitant and background medications

2.1.3 Other objectives

The other objectives are to evaluate the effects of CZP on:

- Spinal mobility
- Total and nocturnal spinal pain (NRS)
- Spinal inflammation
- SI joint structural changes
- Treatment response over time

- Signs and symptoms of the disease
  - Morning stiffness
  - Fatigue
  - Extra articular manifestations of axSpA
  - Sleep
  - Physical function
- Subject's health status
- Acute phase reactant (CRP)
- Health-related quality of life
- Work and household productivity
- Pharmacokinetics and immunogenicity

2.1.4 Pharmacogenomics objectives

The pharmacogenomics objectives are to explore the efficacy of CZP on:

- Relationship between gene and protein expression and genetic/epigenetic biomarkers and response to treatment with CZP (for those subjects who consent to the genomics sub-study)

2.2 Study variables

2.2.1 Efficacy variables

2.2.1.1 Primary efficacy variable

- ASDAS-MI response at Week 52

2.2.1.2 Secondary efficacy variables

- ASAS40 response at Weeks 12 and 52
- Change from Baseline in BASFI at Weeks 12 and 52
- Change from Baseline in BASDAI at Weeks 12 and 52
- Change from Baseline in SI SPARCC score at Week 12
- Number of subjects without relevant changes to background medication

2.2.1.3 Other efficacy variables

The following variables will be analyzed at scheduled time points through Week 52:

- ASAS20, ASAS40, ASAS5/6, and ASAS partial remission response
- Change from Baseline in individual ASAS components:
  - Patient's Global Assessment of Disease Activity (PGADA)
  - Total and nocturnal spinal (NRS)
  - BASFI

  - Average of questions 5 and 6 of the BASDAI concerning morning stiffness
  - BASMI linear
  - CRP
- Change from Baseline in BASDAI and individual questions 1, 2, 3 and 4
- ASDAS disease activity (ASDAS-ID, ASDAS-MD, ASDAS-HD, ASDAS-vHD) and clinical improvement (ASDAS-CII, ASDAS-MI)
- BASDAI50 response
- Change from Baseline in Fatigue (NRS) (from BASDAI)
- Change from Baseline in sacroiliac SPARCC score at Week 52 and ASspiMRI-a in the Berlin modification at Week 12 and Week 52
- Proportion of subjects with sacroiliac SPARCC score <2 at Week 12 and Week 52
- Change from Baseline in ASQoL
- Change from Baseline in ASAS-NSAID score
- Number of uveitis flares
- Number of inflammatory bowel disease exacerbations
- Number of psoriasis exacerbations
- Work Productivity Survey (WPS)
- Change from Baseline in the Sleep Problems Index II domains of the MOS Sleep scale
- Change from Baseline in enthesitis (MASES)
- Change from Baseline in swollen and tender joint counts (44 joint count)
- Change from Baseline in Physician's Global Assessment of Disease Activity (PhGADA)
- Change from Baseline in the SF-36 PCS and MCS
- Change from Baseline in the SF-36 domains:
  - Role Physical
  - Bodily Pain
  - General Health
  - Vitality
  - Social Functioning
  - Role Emotional
  - Mental Health
- Health status as assessed by the EuroQoL Health Status Questionnaire (5 dimensions) (EQ-5D) domains, VAS actual score, and change from Baseline in VAS score

- Resources utilization: concomitant medical procedures, health care provider consultations not foreseen by the protocol, hospitalizations/emergency room visits

2.2.2 Pharmacokinetic/pharmacogenomics variables and biomarkers

2.2.2.1 Pharmacokinetic variables

CZP plasma concentrations will be measured and summarized at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52 and end of study Completion/Withdrawal Visit, and at the SFU visit 10 weeks after the last dose of study medication

These plasma samples may be used additionally for analyses of CZP, its constituent moieties using alternative methods.

2.2.2.2 Biomarkers and cytokines

Selected samples collected for measurement of CZP plasma concentration may be used additionally for analyses of candidate biomarkers and cytokines, where appropriate. The biomarkers to be analyzed may include, but will not be limited to, the following:

Matrix metalloproteinase-3 (MMP-3), Bone morphogenic protein BMP-2,-4 and -7, wingless related mouse mammary tumor virus integration site protein (WNT1) - Inducible Signaling Pathway proteins (WISP), Gremlin, Dickkopf-related protein 1 (DKK1), Sclerostin, Hedgehog proteins (Shh, Ihh, Dhh), Collagen turnover/cleavage products, collagen type X, Vascular Endothelial Growth Factor (VEGF), citrullinated vimentin fragments, cytokines: IL13, IL17 A and F, IL23, IL34, Transforming Growth Factor (TGF) β, Macrophage colony-stimulating factors (M-CSF), Granulocyte macrophage colony-stimulating factor (GM-CS), colony-stimulating factor -1 (CSF-1), soluble CSF-1 Receptor (sCSF1r) levels.

2.2.2.3 Pharmacogenomics variables

For individuals consenting to the genomics substudy, blood samples will be drawn for possible genetic/epigenetic, genomic, and proteomic analysis at Baseline, and, for genomic and proteomics analysis only, at Baseline, Weeks 6, 12, 24, and 52 to enable exploratory evaluation of biomarkers relative to disease biology, drug treatment and inflammatory and immune response processes. The nature and format of these tentative analyses will be determined when the results of the main study are made available. The samples will be stored at -80°C at the central biorepository for up to 20 years.

2.2.3 Immunological variables

Anti-CZP antibody (ADAb) concentrations will be measured and summarized at Baseline, Weeks 1, 2, 4, 12, 24, 36, 52 and end of study Completion/Withdrawal Visit, and the Safety Follow Up (SFU) visit. The number and percentage of subjects with anti-CZP antibody concentrations above 2.4 units/mL will be reported as follows:

- Number and percentage of subjects with ADAb >2.4 units/mL at the time of each visit
- Number and percentage of subjects with ADAb >2.4 units/mL at any visit during treatment (not including post treatment withdrawal or follow up visits)
- Number and percentage of subjects with ADAb >2.4 units/mL at any visit including post treatment withdrawal or follow up visits

2.2.4 Safety variable(s)

2.2.4.1 Adverse events

Presence (Y/N) of

- AE
- Serious AE
- Non-serious AE
- Death
- AE leading to permanent withdrawal of study medication
- Severe AE
- Drug-related AE
- Injection reactions
  - Injection site reactions
  - Systemic injection reactions
    - Acute systemic injection reactions
    - Delayed systemic injection reactions
- AE of special interest
  - Serious infections including opportunistic infections
  - Malignancies including lymphoma
  - Congestive heart failure
  - Demyelinating-like disorders
  - Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia and leucopenia
  - Serious bleeding events
  - Lupus and lupus-like illness
  - Serious skin reactions (eg, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

2.2.4.2 Laboratory parameters

- Change from Baseline in hematology parameters at Weeks 2, 4, 8, 12, 24, 36, 52, end of study completion/early withdrawal visit, and the SFU visit 10 weeks after the last dose of study medication
  - Red blood cells
  - Hemoglobin
  - Hematocrit

  - Platelets
  - White blood cells
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
- Change from Baseline in hematology parameters to minimum post-Baseline value, maximum post-Baseline value, and last value
  - Red blood cells
  - Hemoglobin
  - Hematocrit
  - Platelets
  - White blood cells
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
- Change from Baseline in serum biochemistry parameters Weeks 2, 4, 8, 12, 24, 36, 52 end of study completion/early withdrawal visit, and the SFU visit 10 weeks after the last dose of study medication
  - Sodium
  - Potassium
  - Chloride
  - Bicarbonate
  - Total calcium
  - Inorganic phosphorus
  - CRP (already included in efficacy section)
  - Creatinine kinase (CK)
  - Glucose
  - Creatinine

  - Uric acid
  - Urea
  - Total protein
  - Albumin
  - Alkaline phosphatase (AP)
  - Aspartate aminotransferase (AST)
  - Alanine aminotransferase (ALT)
  - Bilirubin
  - Total cholesterol
- Change from Baseline in serum biochemistry parameters to minimum post-Baseline value, maximum post-Baseline value, and last value
  - Sodium
  - Potassium
  - Chloride
  - Bicarbonate
  - Total calcium
  - Inorganic phosphorus
  - CRP (already included in efficacy section)
  - Creatinine kinase (CK)
  - Glucose
  - Creatinine
  - Uric acid
  - Urea
  - Total protein
  - Albumin
  - Alkaline phosphatase (AP)
  - Aspartate aminotransferase (AST)
  - Alanine aminotransferase (ALT)
  - Bilirubin
  - Total cholesterol
- Urinalysis status at Weeks 2, 4, 8, 12, 24, 36, 52, end of study completion/early withdrawal visit, and the SFU visit 10 weeks after the last dose of study medication

  - PH
  - Protein
  - Glucose
  - Blood
  - Esterase
- Hematology parameter normal range classification at Weeks 2, 4, 8, 12, 24, 36, 52, end of study completion/early withdrawal visit, and the SFU visit 10 weeks after the last dose of study medication
  - Red blood cells
  - Hemoglobin
  - Hematocrit
  - Platelets
  - White blood cells
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
- Serum biochemistry parameter normal range classification at Weeks 2, 4, 8, 12, 24, 36, 52, end of study completion/early withdrawal visit, and the SFU visit 10 weeks after the last dose of study medication
  - Sodium
  - Potassium
  - Chloride
  - Bicarbonate
  - Total calcium
  - Inorganic phosphorus
  - CRP (already included in efficacy section)
  - Creatinine kinase
  - Glucose
  - Creatinine
  - Uric acid

  - Urea
  - Total protein
  - Albumin
  - Alkaline phosphatase
  - Gamma glutamyl tranferase
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Bilirubin
  - Total cholesterol
- Hematology parameter marked abnormality classification (Rheumatology Common Toxicity Criteria [RCTC]) Weeks 2, 4, 8, 12, 24, 36, 52, end of study completion/early withdrawal visit, and the SFU visit 10 weeks after the last dose of study medication
  - Hemoglobin
  - Platelets
  - White blood cells
  - Neutrophils
  - Lymphocytes
- Serum biochemistry parameter marked abnormality classification (RCTC) Weeks 2, 4, 8, 12, 24, 36, 52, end of study completion/early withdrawal visit, and the SFU visit 10 weeks after the last dose of study medication
  - Sodium
  - Potassium
  - Total calcium
  - Creatinine kinase
  - Glucose
  - Creatinine
  - Uric acid
  - Alkaline phosphatase
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Bilirubin
- Presence (Y/N) of liver parameter elevations above upper limit of normal (ULN)

- 3x ULN elevations of AST
- 5x ULN elevations of AST
- 10x ULN elevations of AST
- 20x ULN elevations of AST
- 3x ULN elevations of ALT
- 5x ULN elevations of ALT
- 10x ULN elevations of ALT
- 20x ULN elevations of ALT
- 3x ULN elevations of either AST or ALT
- 5x ULN elevations of either AST or ALT
- 10x ULN elevations of either AST or ALT
- 20x ULN elevations of either AST or ALT
- 1x ULN elevations of bilirubin
- 1.5x ULN elevations of bilirubin
- 1.5x ULN elevations of AP
- 1x ULN elevation of bilirubin and 3x ULN elevation of either ALT or AST

2.2.4.3 Vital signs

- Change from Baseline in vital signs at Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44 , 46, 48, 50, 52, end of study completion/early withdrawal visit, and the SFU visit 10 weeks after the last dose of study medication
  - Pulse rate
  - Systolic blood pressure
  - Diastolic blood pressure
  - Temperature
  - Respiration rate
- Change from Baseline in vital signs to minimum post-Baseline value, maximum post-Baseline value, and last value
  - Pulse rate
  - Systolic blood pressure
  - Diastolic blood pressure
  - Temperature
  - Respiration rate

2.2.4.4 Other safety variables

- Change from Baseline in weight at Weeks 12, 16, 24, completion at Week 52/early withdrawal visit
- Signs and symptom of latent or active TB completed at Baseline, Weeks 12, 24, 36, 52 and end of study completion/early withdrawal visit
- TB risk factors
- Occurrence of pregnancy through to Week 52/Withdrawal and Safety Follow Up

2.3 Study design and conduct

AS0006 is a 52-week multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study to evaluate the efficacy and safety of CZP in adult subjects with active axSpA with sacroiliitis on magnetic resonance imaging (MRI) or CRP levels indicative of inflammatory disease but without x-ray evidence of ankylosing spondylitis (AS) who have had an inadequate response to, have a contraindication to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

2.3.1 Study periods

Period 1 (Screening Period) – Screening period of 1 to 6 weeks before baseline in order to obtain laboratory data, to verify that the doses of methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), NSAIDs, and corticosteroids, if used, are stable, and to enable washout of any medications not permitted for use during the study, and initiation of latent TB treatment where necessary. Concomitant medications permitted during the study should remain stable for at least 12 weeks prior to Baseline.

SI-joint x-rays (read centrally) will allow discrimination of subjects with (AS) and without definitive evidence for sacroiliitis on x-ray (mNY-negative-axSpA).

Enrolled subjects must undergo an MRI later during the Screening Period for central reading with results from the central reading available by no later than at the Baseline visit.

Period 2 (Double-Blind Period) – Week 0 to Week 52, placebo-controlled.

Eligible subjects will be allocated to the following study treatments in a 1:1 ratio:

- CZP administered at the loading dose of CZP 400mg Q2W at Weeks 0, 2 and 4 followed by CZP 200mg Q2W (starting at Week 6)
- Placebo

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), study treatments (including placebo) will be administered sc at the study site by dedicated unblinded trained site personnel throughout the study. The study treatment will be self-injected at home at Weeks 10, 14, 18, 22, 26, 30, 34, 38, 42, and 46. All subjects will receive training for self-injection at the study site on Weeks 6 and 8. During the training on Weeks 6 and 8 visits, the study treatment will be self-administered under the supervision of the unblinded study personnel.

Period 3 (Safety Follow-up [SFU] Period):

All subjects, including those withdrawn from study treatment, will have a SFU Visit 10 weeks after their last administration of study medication.

The schedule of study assessments is provided in Section 5.2 of the protocol.

A schematic diagram of the study design is provided in Section 5.3 of the protocol.

2.3.2 Study duration per subject

For each subject, the study will last a maximum of 66 weeks, as follows:

- Up to 6 weeks in the Screening Period
- 52 weeks in the Double-Blind Period
- A SFU Visit 10 weeks after last dose administration (ie, Week 50, if the subject completed the entire dose administration schedule)

2.3.3 End of periods and study

The end of the study is defined as the date of the last visit (SFU) of the last subject in the study.

2.3.4 Planned number of subjects and sites

Approximately 900 subjects are expected to enter the Screening Period in order to have 300 subjects randomized into the study. It is planned to enroll the subjects at approximately 80 sites.

2.3.5 Anticipated regions and countries

The study will be conducted in North America, Australia, Europe, and other regions as appropriate.

2.3.6 Stratification

Randomization will be stratified on:

- Site
- MRI/CRP classification

Subjects will be classified as MRI+/- depending on whether or not they have evidence of sacroiliitis on MRI at Screening based on the ASAS/OMERACT definition. Subjects will be classified as CRP+/- based on the CRP value obtained at the second Screening visit scheduled to occur 3 to 5 days prior to Baseline. Subjects will be categorized as CRP+ if their CRP value is above the level indicative of inflammatory disease at this visit. Otherwise, they will be considered CRP-. Based on these definitions, the stratification for MRI/CRP classification will have the following 3 levels:

- MRI+/CRP+
- MRI+/CRP-
- MRI-/CRP+

Subjects who are MRI-/CRP- are not eligible for randomization. The IVRS will be designed to ensure that at least 20% and no more than 40% of the randomized subjects belong to one of the three clinical subgroups above.

2.4 Determination of sample size

Subjects will be randomized in a 1:1 ratio to the CZP 200mg Q2W and placebo treatment groups. The expected response rates for ASDAS-MI at Week 52 are 40% and 20% for CZP and placebo, respectively. A total sample size of 300 (150 subjects per treatment group) provides 90% power to detect a statistically significant difference in the ASDAS-MI response rate at Week 52 between CZP and placebo based on a 2-sided significance level of 0.05.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

All statistical analyses will be performed using SAS® (STATISTICAL ANALYSIS SYSTEM, SAS-Institute, Cary, NC, USA) according to UCB SOPs.

For continuous data in general, summary statistics (n [number of available measurements], arithmetic mean, SD, median, minimum, and maximum) will be presented by treatment group. For selected variables, Q1 and Q3 will also be presented.

Mean, SD, and median will be displayed to 1 more decimal place than collected in the case report form (CRF) or than the rounded calculated variable.

For descriptive statistics of continuous variables by visit, the change from Baseline and actual value at the given time point will be displayed.

Frequency tables (frequency counts and percentages) will be presented for categorical data. If there are missing values, either a missing category will be included in the display or the number of non-missing results will be used for calculations.

If imputation is performed, summary statistics will not utilize the 'n' (number of available measurements).

In general, percentages will be calculated based on the utilized analysis set. However, in the case of subgroup analyses, the N of the subgroup will be used as denominator.

Unless stated otherwise, all inferential statistical tests will be 2-sided and conducted at the 0.05 alpha level. P-values will be presented to 3 decimal places. Relevant SAS output will be included in the 'Documentation of Statistical Methods' section of the CSR.

The change from Baseline is the post-Baseline value minus the Baseline value. If the Baseline or post-Baseline value is missing, then the change from Baseline is set to missing. Percent change from Baseline is the change from Baseline divided by Baseline and multiplied by 100. If the Baseline value is 0 and the post-Baseline value is also 0, then the percent change from Baseline is set to 0. If the Baseline value is 0 and the post-Baseline value is non-zero, then the percent change from Baseline is set to missing. If the Baseline value is missing, the percent change from Baseline is set to missing.

All data in the database (SDTM and ADaM) will be presented in by-subject data listings, and sorted by treatment group, site, subject number, and visit (where applicable).

A fixed-sequence testing procedure will be used to control the overall Type 1 error for comparison of multiple efficacy endpoints. This procedure is described in Section 8.

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 Pre-treatment period

The pre-treatment period (Screening period) of the study is the period prior to a subject's first dose of study medication intake. This period starts at the Screening visit (week -5 to -1) and ends at the Baseline visit (Week 0) up to the time of first study medication administration (exclusive). Unless specific time information is available to indicate that a Screening or Baseline visit assessment was performed after a subject's first study medication administration, all assessments will be attributed to the Screening period.

3.2.1.2 Double-blind treatment period

The Double-Blind Treatment Period begins at the Baseline visit (Week 0) at the time of first study medication administration (inclusive) and ends at Week 52 visit. The SFU visit will take place 10 weeks after the last dose of study medication, which will be 8 weeks after the Week 52 visit (if the Week 52 is the last non-SFU visit) or less than 10 weeks after the W/D visit (if the W/D visit is the last non-SFU visit).

Premature withdrawal visit assessments will be assigned to the next scheduled visit following the last visit where assessments were available. All visit measurements, even violating the visit window, will be utilized for the respective visit as long as they are in the proper sequence.

3.2.2 Relative day

The relative day will be included in different listings and will be calculated as follows:

- If the start (stop) date occurred on or after the first dose, but prior to the drug stop date, relative day is calculated as start (stop) date minus first dose date + 1
- If the start (stop) date occurred after the last dose, the relative day to the most recent dose is calculated as start (stop) date minus most recent dose date. The relative day in this situation should be preceded by a '+'.
- If the start (stop) date occurred before the first dose, the relative day is calculated as start (stop) date minus first dose date. The relative day in this situation should be preceded by a '-'.

For AEs, relative days for start and stop dates will be calculated as the number of days since the first injection of the medication. For non-treatment emergent AEs, relative day of onset will be negative if the event started and stopped before the first dose.

3.3 Definition of Baseline values

Unless otherwise specified, the last valid measurement before study medication administration will be used as the Baseline value. For almost all variables, this will be the assessment made at the Baseline visit. However, for some variables (eg, demography) assessments are scheduled for the Screening visit only and not for the Baseline visit. In this case, the Screening value will be utilized as Baseline value.

Baseline images, either spinal x-ray or MRI assessments, are required to evaluate study elibiglity. Therefore, all Baseline images will be available prior to randomization into the study.

SI joint x-rays should not be older than 12 months prior to Baseline and should be verified by central reading during the Screening Period.

If a Baseline measurement is missing, and a Screening value available, the Screening value will be utilized as Baseline instead.

Unless otherwise specified, for subjects with missing continuous or discrete efficacy Baseline values which cannot be imputed by Screening values, Baseline will be imputed by the median Baseline value of the available subjects within the stratum for MRI/CRP classification. For discrete variables, the imputed values will be rounded to the nearest integer. Unless otherwise specified, with regard to categorized endpoints, the outcome with the highest frequency within this stratum will be applied (in case of ties, the least severe category will be used).

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on study conduct or on the primary efficacy outcome for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented prior to unblinding to confirm exclusion from analysis sets.

3.5 Analysis sets

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have given informed consent.

3.5.2 Randomized Set

The Randomized Set (RS) will consist of all subjects randomized into the study.

3.5.3 Safety Set

The Safety Set (SS) will consist of all subjects in the RS who have received at least one dose of study medication.

3.5.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the RS who have received at least 1 dose of study medication, have a valid Baseline, and have a valid post-Baseline efficacy measurement for ASDAS.

3.5.5 Per Protocol Set

The Per-Protocol Set (PPS) will consist of subjects in the FAS without any important protocol deviations that may influence the validity of the data for the primary efficacy variable.

3.6 Treatment assignment and treatment groups

At Baseline the following treatments were randomly assigned in a 1:1 ratio:

- Placebo (PBO)
- CZP administered at the loading dose of CZP 400mg Q2W at Weeks 0, 2 and 4 followed by CZP 200mg Q2W (starting at Week 6)

For presentation purposes, the terms CZP 200mg Q2W and PBO will be used.

For demography and Baseline characteristics, in addition to the PBO and CZP 200mg, an overall group (PBO and CZP 200mg) will be displayed.

If it is determined after unblinding that the subjects received a treatment other than the one to which they were randomized, safety tables will still be based on the randomized treatment for the SS. However, additional safety tables based on the actual treatment received will be prepared. For these tables, placebo subjects receiving CZP in error will be displayed utilizing their data as CZP data beginning with the first intake of CZP. Placebo data until the time that CZP treatment was incorrectly given will still be allocated to the placebo group. CZP subjects incorrectly treated with placebo will stay in the CZP group.

The efficacy analyses will strictly follow the intention to treat principle, and no correction for incorrect treatment will be performed.

3.7 Center pooling strategy

Due to the planned limited number of subjects per center, it will be inappropriate to include the factor center in the statistical model. Instead the factor region will be utilized and defined as reasonable combination of centers prior to unblinding.

3.8 Coding dictionaries

Medical history and AEs will be coded using the latest version at the time of study lock of Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Reference List (WHO-DRL).

3.9 Changes to protocol-defined analyses

Not applicable.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

Statistical models may be adjusted for covariates. Any such adjustments will be described in the context of the analyses to be performed.

4.2 Handling of dropouts or missing data

For analysis purposes, the primary efficacy variable is defined as a composite endpoint in which it is necessary to achieve ASDAS-MI at Week 52 and to remain on randomized study treatment through Week 52 in order to be considered a responder. Because this composite endpoint definition does not allow for a missing response status, no formal method for handling missing data is needed in the primary analysis. An additional analysis will be performed in which all observed data at Week 52 are used, including data collected for subjects who may have discontinued study treatment without being withdrawn from the study.

Analyses of other binary efficacy variables will be treated in the same way as the primary efficacy variable. That is, a subject will be considered a responder only if the response is achieved and if the subject is still on their randomized study treatment at the time when the variable is evaluated.

For continuous secondary efficacy variables, the analysis method that will be used when considering statistical significance in the fixed sequence testing procedure will be based on a mixed effects model for repeated measurements (MMRM), unless otherwise specified. As an alternative approach to handling missing data, the analyses of these secondary efficacy variables will also be performed using LOCF imputation for comparative purposes.

The analysis of continuous variables derived from MRI at Week 12 will be based only on the observed values (ie, observed case analysis). At Week 52, continuous MRI variables will be analyzed using MMRM.

Descriptive summaries based on observed case data will also be prepared.

These methods will be applied in general unless otherwise specified. Additionally, algorithms for imputing missing or partial dates for safety evaluations are detailed where relevant in other sections of this document.

4.3 Interim analyses and data monitoring

No interim analysis is planned for this study.

Regular monitoring of safety data collected during the study will be performed as described in the Safety Signal Detection in the Ongoing Clinical Trials Charter for CZP.

A specific data monitoring-, steering-, or evaluation-committee is not planned for this study.

4.4 Multicenter studies

With the exception of disposition data and important protocol deviations, results will not be presented by individual center. However, the sites will be pooled to regions and utilized for analysis and display of results.

4.5 Multiple comparisons/multiplicity

The statistical analysis of the primary efficacy variable and selected secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure. The predefined order of hypotheses testing, each at a 2-sided 0.05 significance level for the comparison between CZP 200mg Q2W and placebo, will be performed in the sequence shown below. After the first test, each subsequent test is performed only if the previous test is significant in favor of CZP at the 2-sided 0.05 level. Note that the first test relates to the primary efficacy variable while the others provide the sequence testing for selected secondary efficacy variables.

1. ASDAS-MI response at Week 52
2. ASAS40 response at Week 12
3. Change from Baseline in BASDAI at Week 12
4. Change from Baseline in BASFI at Week 12
5. Change from Baseline in SI joint SPARCC score at Week 12
6. ASAS40 response at Week 52
7. Change from Baseline in BASDAI at Week 52
8. Change from Baseline in BASFI at Week 52

4.6 Use of an efficacy subset of subjects

The PPS will be used to evaluate subjects who have efficacy data during the Double-Blind Treatment Period and are reasonably compliant with the conditions of the study. This analysis set will provide additional information on the efficacy analysis and will describe findings in a subset of subjects who more closely follow the intentions of the study protocol.

Other than the planned analyses based on the PPS, no other efficacy subsets are defined for statistical analyses.

4.7 Active-control studies intended to show equivalence

Not applicable.

4.8 Examination of subgroups

Subgroups for age, gender, race, symptom duration, smoking history, HLA-B27 genotype, region, prior anti-TNF exposure, anti-CZP antibody status (> or < 2.4 units/mL), and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) will be utilized for the analysis of the primary efficacy variable. Additionally, the secondary efficacy variables will be summarized by the MRI/CRP classification.

Age, in contrast to the demographic data display, will be condensed for the purpose of subgroup analysis into 2 groups (<45 and ≥45 years). The same is true for race, where only the 2 categories white and non-white will be considered. Symptom duration will be classified into <5 and ≥5 years. Prior anti-TNF exposure will be classified into Yes/No.

Start date of chronic back pain (primary symptom) will be utilized to calculate the symptom duration.

- If no information about the start date of the chronic back pain is available, it will be imputed with the available start date of the primary disease.
- If the start date of the primary disease is also missing, it will be imputed using the following rules:
  - If day is missing, day will be replaced by first of the month
  - If month is missing, month will be replaced by January
  - If year is missing, the median duration of the subjects that have a valid symptom duration within the same stratum regarding MRI/CRP classification will be used to calculate the missing start date.
  - If the resulting symptom duration is less than 3 months, the imputed start date will be set to the latest date with a minimum symptom duration of 3 months and 1 day.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number of subjects screened, randomized, completed, prematurely discontinued study treatment, prematurely discontinued study, and reason for premature discontinuation of study treatment and study will be summarized by treatment group. The number of subjects who

complete each visit (as captured in the CRF) will also be summarized. In addition, the number of subjects in each of the analysis sets, as specified in Section 3.5, will be summarized as well.

5.2 Protocol deviations

The process for reviewing and identifying important protocol deviations is outlined in Section 3.4. The number of subjects with at least one important protocol deviation will be summarized by treatment group. This summary will be performed for all subjects and will also be broken out by study center.

The subject data listing, in contrast to the general approach (ie, sorted by treatment group, site, subject number), will be sorted by site, treatment group, and subject number.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

The demographics and other Baseline characteristics will be presented for the RS. If the RS differs from the SS or the FAS, then demographics and Baseline characteristics tables may be repeated separately for these analysis sets. These summaries will be presented by treatment group and all subjects.

Tables on medical history and prior diseases, and concomitant and prior medications will also be presented.

6.1 Demographics

The following continuous demographic variables will be summarized:

- Age (years)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

The following categorical demographic variables will also be summarized:

- Gender (Female, Male),
- Race (American Indian / Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other / Mixed),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino),
- Racial subgroup: (Indian / Pakistani / Middle Eastern, Other),
- Age class (to be summarized 3 ways: 1) ≤18, >18 to <65 years, and ≥65 years; 2) <45 years and ≥45 years; and 3) ≤18, 19 – 24 years, 25 – 34 years, 35 – 44 years, 45 – 54 years, 55 – 64 years, 65 – 74 years, and ≥75 years),
- BMI class (<18.5 kg/m^2, 18.5 kg/m^2 to <25 kg/m^2, 25 kg/m^2 to <30 kg/m^2, ≥30 kg/m^2)

6.2 Other Baseline characteristics

In this section, the variables that will be summarized as Baseline characteristic are described.

It will be expected, that all subjects fulfill the modified ASAS Criteria. The different binary items of the criteria will be presented in frequency tables:

- back pain of ≥ 3 month duration at age of onset < 45
- active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- definitive sacroiliitis (grade ≥ 2 bilaterally or ≥3 unilaterally)
- 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

Symptom duration will be summarized as a continuous variable. It will also be summarized as a dichotomized variable where symptom duration is split as <5 years and ≥5 years.

Frequency tables will be provided for the following Baseline variables related to TB status:

- Contact with an individual with active TB
- Contact with an individual who has recently been treated for TB

Summary statistics will be provided for the laboratory variable CRP. Additionally, CRP will be categorized based on the number of subjects with CRP ≤15mg/L and >15mg/L.

Frequency tables will summarize HLA-B27, the test at Screening to rule out hepatitis B surface antigen, and the test at Screening to rule out antibodies to hepatitis C.

Frequencies will also be provided for subjects with the following:

- Peripheral arthritis (swollen joint count > 0) at Baseline
- Enthesitis (MASES > 0)
- Extra-articular manifestations:
  - History of uveitis
  - History of psoriasis
  - History of IBD
- Concomitant DMARDs at Baseline

- Prior DMARDs and prior NSAIDs
- Region
- MRI/CRP classification (as used for stratification at randomization):
  - MRI+/CRP+
  - MRI+/CRP-
  - MRI-/CRP+

Note that the term DMARDs is used above as it is common to rheumatic diseases. However, there is currently no conclusive evidence that DMARDs are in fact disease-modifying in axSpA (unlike in RA). As a result, the term SAARDs (slow-acting anti-rheumatic drugs) is used in the protocol to refer to this class of medications. The DMARDs terminology is generally used in this SAP, but it is recognized that SAARDs may be more appropriate in the context of a study of subjects with axSpA.

Since the procedures and surgeries in the procedural history will not be coded, these data will only be presented in listings.

Baseline information for other key measures related to axSpA (eg, BASFI, BASDAI, BASMI, and ASDAS) will be presented in the respective tables providing descriptive statistics over time.

6.3 Medical history and concomitant diseases

Previous and ongoing medical history will be summarized by MedDRA® system organ class (SOC) and preferred term (PT). Medical procedures are not coded. Concomitant diseases will be recorded by the Investigator at the Screening Visit only.

6.4 Prior and concomitant medications

Prior medications include any medications that started prior to the start date of study medication. Past medications are a subset of prior medications, and include prior medications with a stop date before the date of first study medication administration. Concomitant medications are medications taken at least one day in common with the study medication dosing period. The dosing period will be defined as the date of first dose up to (but not including) 14 days post last dose. Thus, a concomitant medication is any medication whose start date is on or after the date of first study medication and prior to the date of last study medication administration + 14 days, and whose stop date is either missing, or on or after the date of first study medication administration. Medications may be both prior and concomitant.

Where a medication start date is (partially) missing, the medication will be considered a concomitant medication, if there is the possibility of concomitant use.

The following rules are based on the assumption that if the start date is incomplete, either day only is missing, or day and months are missing, or date is completely missing.

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of the start date, then use the 1st of the month.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start, then use the date of first dose.

- If only the year is specified, and the year of first dose is not the same as the year of the start date, then use January 1 of the year of the start date.
- If only the year is specified, and the year of first dose is the same as the year of the start date, then use the date of first dose.
- If the start date is completely unknown, then use the date of first dose.

If the medication is not ongoing (stopped) and the stop date is incomplete or missing, the following rules will be utilized (assuming again, that day, day and month, or complete date is missing):

- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then use December 31 of that year.
- If the stop date is completely unknown, do not impute the stop date (Note: If an end date is needed for purposes of evaluating a protocol deviation, a "worst case" approach will be applied. That is, a protocol deviation will be assumed so long as the medication could have possibly been taken in the window necessary to meet the deviation criteria.)

If there are incomplete dates not covered by the rules above (eg, only month is missing and day and year are available), individual definitions will be made prior to unblinding.

Past medication summaries will be generated for DMARDs, NSAIDs, and Anti-TNFs by ATC code (level 3 (4-digit) decode, level 4 (5-digit) decode, and Preferred Term).

Prior DMARDs and NSAIDs will be summarized by ATC code (level 3 (4-digit) decode, level 4 (5-digit) decode, and Preferred Term). No extra table for prior Anti-TNFs will be produced due to the fact that this summary is identical to the 1 for the past Anti-TNF.

Prior medication (except DMARDs and NSAIDs) will be summarized by ATC code (level 2 (3-digit) and level 3 (4-digit) decode.

Concomitant DMARDs and NSAIDs will be summarized by ATC code (level 3 (4-digit) decode, level 4 (5-digit) decode, and Preferred Term).

Concomitant medication (except DMARDs and NSAIDs) will be summarized by ATC code (level 2 (3-digit) and level 3 (4-digit) decode.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

There will be 2 approaches to calculate treatment compliance. The first will utilize the number of administered syringes and compare them to the scheduled expected number of injections. The sum of the difference in number of syringes between the actual used and expected syringes will be summarized. In addition, a ratio of compliance will be further computed based on the number of actual and expected syringes. The ratio of compliance will be summarized as a continuous variable and categorically (<0.80 and ≥0.80). The general formula for the compliance ratio (CR) is given as follows:

CR = # actual syringes / # expected syringes

The second approach defines compliance with study drug administration based upon comparing the actual day of administration with the expected day of administration. The expected day of

administration will be based upon the Baseline date. The sum of the absolute difference in days between the actual and expected days will be summarized. In addition, a ratio of compliance will be further computed based upon the actual and expected day. The ratio of compliance will also be summarized as a continuous variable and categorically (<0.80 and ≥0.80). The general formula for the compliance ratio is given as follows:

CR = (Study Duration - Cumulative Difference) / Study Duration

The CR ranges between 0 and 1.

To calculate study duration, the date of the Week 50 visit or the last injection date prior to study treatment discontinuation will be compared to the Baseline date, as shown below:

Study Duration (days) = Week 50 visit/last injection date – Baseline date (maximum value is 350 days)

Cumulative Difference (days) = sum (ABS [actual date – scheduled date])

The sum will be calculated for the 26 visits from Week 0 (Baseline) to Week 50.

In case the actual day of administration is missing, the maximum deviation to the scheduled day will be assumed (ie, 14 days). If, for a scheduled day with 2 planned injections, the syringes were administered on 2 different days, the maximum day difference of the 2 actual dates to the scheduled date will be utilized.

8 EFFICACY ANALYSES

All efficacy analyses will be performed using the FAS. The PPS will be used for a sensitivity analysis on the primary endpoint only.

The statistical analysis of the primary efficacy variable and selected secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure. The predefined order of hypotheses testing, each at a 2-sided 0.05 significance level for the comparison between CZP 200mg Q2W and placebo, will be performed in the sequence shown below. After the first test, each subsequent test is performed only if the previous test is significant in favor of CZP at the 2-sided 0.05 level. Note that the first test relates to the primary efficacy variable while the others provide the sequence testing for selected secondary efficacy variables:

1. ASDAS-MI response at Week 52
2. ASAS40 response at Week 12
3. Change from Baseline in BASDAI at Week 12
4. Change from Baseline in BASFI at Week 12
5. Change from Baseline in SI joint SPARCC score at Week 12
6. ASAS40 response at Week 52
7. Change from Baseline in BASDAI at Week 52
8. Change from Baseline in BASFI at Week 52

Variables evaluated over time will be summarized using imputed and observed case values. The approach for handling missing values is described in Section 4.2.

The results of fixed sequence testing procedure will be summarized in a table.

8.1 Statistical analysis of the primary efficacy variable

The primary efficacy variable measurement for this study is based on ASDAS-MI response at Week 52. However, the primary outcome of the study will be defined as a composite endpoint that is achieved if a subject fulfills the following 2 components:

1. Remain in the study and on study treatment through 52 weeks
2. Achieve an ASDAS-MI response at 52 weeks

For simplicity, this primary efficacy variable will be referred to as ASDAS-MI response at Week 52. However, the composite definition as described above will apply when this endpoint is analyzed.

8.1.1 Derivation of primary efficacy variable

The ASDAS is comprised of a number of assessments which are scored by the subject and physician and multiplied by a proven formula (van der Heijde et al, 2008) as listed:

- 0.121 x Back pain (BASDAI Q2 result)
- 0.058 x Duration of morning stiffness (BASDAI Q6 result)
- 0.110 x Patient's Global Assessment of Disease Activity (PGADA)
- 0.073 x Peripheral pain/swelling (BASDAI Q3 result)
- 0.579 x (natural logarithm of the (CRP [mg/L]+ 1))

Back pain, PGADA, duration of morning stiffness, peripheral pain/swelling and fatigue are all assessed on a numerical scale (0 to 10 units) (Lukas et al, 2009).

The sum of these weighted components gives the ASDAS.

If 1 component for the ASDAS is missing at a given visit, that component will be imputed by carrying the last observation forward, and the ASDAS will be calculated accordingly. If no value is available for that component before the missing time point, the next observation may be carried backwards. If more than one component for the ASDAS is missing, ASDAS will be treated as missing.

If the CRP value is below the lower limit of quantification (LLOQ) or below 2mg/L, then it will be imputed as 2mg/L (Machado et al, 2014).

Disease activity categories based on ASDAS are as follows:

- ASDAS-Inactive Disease (ASDAS-ID): ASDAS <1.3
- ASDAS-Moderate Disease (ASDAS-MD): ASDAS >=1.3, <2.1
- ASDAS-High Disease Activity (ASDAS-HD): ASDAS >=2.1, <=3.5
- ASDAS-very High Disease Activity (ASDAS-vHD): ASDAS >3.5

The variables related to ASDAS improvement are defined as follows:

- ASDAS-Clinically Important Improvement (ASDAS-CII): ASDAS reduction (improvement) of >=1.1 relative to Baseline
- ASDAS-Major Improvement (ASDAS-MI): ASDAS reduction (improvement) of >=2.0 relative to Baseline

8.1.2 Primary analysis of the primary efficacy variable

The primary analysis for of the primary efficacy variable will be based on logistic regression. The odds ratio of the ASDAS-MI responder rates at Week 52 will be estimated and tested between treatment groups using a logistic regression model with factors of treatment group, region, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+). The study design is likely to result in some sites with a small number of enrolled subjects. The use of region as a factor in the model is intended to combine study centers in similar geographic regions.

Given the composite endpoint definition described in Section 8.1, there will be no missing data for the primary endpoint, as subjects that withdraw prior to Week 52 or who do not have an ASDAS-MI response at Week 52 are considered non-responders to study treatment.

Tables will present the responder rates for placebo and CZP 200mg, the respective effect estimates (adjusted odds ratio with reference to placebo), p-values, and 95% confidence intervals (CIs). These figures will also be presented graphically.

8.1.3 Supportive and sensitivity analyses of the primary efficacy variable

As described in Section 5.3 of the protocol, subjects who discontinue study treatment will not necessarily be withdrawn from the study. In an attempt to minimize missing data, efforts will be made to continue to collect safety and efficacy data on these subjects through study completion. A supportive analysis for ASDAS-MI at Week 52 will be performed in which the observed data at Week 52 will be used, regardless of whether or not the subject is still on their randomized study treatment at that time. Any missing data at Week 52 despite this more rigorous approach to data collection will not be imputed for this analysis. The odds ratio and corresponding 95% CI of the ASDAS-MI responder rates at Week 52 based on the observed data will be estimated and tested between treatment groups using a logistic regression model with factors of treatment group, region, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+).

Subgroup analyses by age, gender, race, symptom duration, smoking history, HLA-B27 genotype, region, prior anti-TNF exposure, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) will be performed for the primary variable.

The PPS will be used for a sensitivity analysis on the primary endpoint.

8.2 Statistical analysis of secondary efficacy variables

The secondary efficacy variables are designated as variables 2 through 8 in the hierarchical testing procedure outlined in Section 8. The statistical methodology to be used for the analysis of these variables is described below.

The changes from Baseline in BASDAI and BASFI at Week 12 and Week 52 (Tests #3, #4, #7, and #8 in the statistical hierarchy) for the FAS will be compared between treatment groups using a mixed model for repeated measures (MMRM).

The pattern of missingness for these variables is assumed to be missing at random (MAR). Investigators will be given discretion to discontinue study treatment for subjects not responding in order to provide them with alternative therapy to treat the condition. Therefore, in most cases, missing efficacy data due to study treatment discontinuation should be dependent on the observed efficacy scores, but independent of unobserved data. The MMRM model will include Baseline score as a fixed-effect covariate, treatment group, region, MRI/CRP classification, and visit as fixed-effect categorical factors, and Baseline-by-visit and treatment group-by-visit as interaction terms. Efficacy data based on assessments after treatment discontinuation will be excluded from this analysis (ie, will be considered missing). An unstructured correlation pattern will be used to estimate the variance-covariance of the within-subject repeated measures.

Change from Baseline in SI joint SPARCC score at Week 12 (Test #5) will be compared between treatment groups using analysis of covariance (ANCOVA) for observed values only (ie, no imputation). The model will include Baseline score, treatment group, region, and MRI/CRP classification. Tables will present the adjusted means for placebo and the CZP dose (200mg Q2W), the respective difference to placebo, the corresponding p-value, and 95% CI. A sensitivity analysis will be performed on the change from Baseline in SPARCC score at Week 12 using the same model including only those subjects that are MRI+ at Baseline.

The ASAS40 response at Weeks 12 and 52 (Tests #2 and #6) will be analyzed using the same approach as described for the primary analysis. Specifically, subjects will need to 1) achieve the ASAS40 response and 2) remain in the study and on their randomized study treatment through the time point being analyzed (Week 12 or Week 52). Note that a subject with a missing value at the Week 12 time point will be considered as not having responded, even if the subject has not discontinued study treatment. Tables and figures for the FAS will be used to display the ASAS40 response at Weeks 12 and 52.

An additional secondary efficacy variable is the number of subjects with relevant changes to background medication (see definition in Section 8.2.1.5). The analysis for this variable will be based on the same logistic regression model described for the primary variable.

In addition to the analyses mentioned above, descriptive statistics (number of available observations [n], mean, median, standard deviation, minimum and maximum) will be provided for the secondary variables. The descriptive analyses will be covered in the tables summarizing the variables over time. Additionally, all secondary efficacy variables will be summarized by MRI/CRP classification (see Section 4.8).

8.2.1 Derivation of secondary efficacy variables

8.2.1.1 Assessment in Axial Spondyloarthritis International Society response criteria (ASAS20/40, ASAS5/6, and ASAS partial remission)

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 numeric rating scale (NRS) in at least 3 of the 4 following domains (Anderson, 2001):

- Patient's Global Assessment of Disease Activity;
- Pain assessment (the total spinal pain NRS score);
- Function (represented by the 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 ASAS criteria for 40% improvement (ie, ASAS40) are defined as relative improvements of at least 40% and absolute improvement of at least 2 units on a 0 to 10 NRS in at least 3 of the 4 domains and no worsening at all in the remaining domain.

The ASAS 5/6 response is defined as at least 20% improvement in 5 of 6 domains, which includes spinal mobility (i.e., lateral spinal flexion, BASMI, see Section 3.9.11) and CRP as more objective measures (Brandt et al, 2004). If the CRP value is below the lower limit of quantification (LLOQ), then it will be imputed as the midpoint between 0 and the LLOQ.

The ASAS partial remission response is defined as a score of ≤2 units on a 0 to 10 unit scale in all 4 domains.

For all non-missed visits, if any of the component scores are missing, then the following rules will be applied:

- If all the component values are missing from Baseline through the visit being considered, the percent improvement from Baseline to that visit for the given component will be imputed as 0%. The unit improvement will be imputed as 0.
- If the component value at a given visit is missing and the Baseline value is present, the missing component will be replaced by the last non-missing observation (LOCF) for that component.

ASAS40 response at Week 12 and Week 52 are secondary efficacy endpoints.

8.2.1.2 Bath Ankylosing Spondylitis Disease Index (BASDAI)

The BASDAI is the most commonly used instrument to measure the disease activity of ankylosing spondylitis. The BASDAI is a validated self-reported instrument which consists of 6 horizontal Numeric Rating Scales (NRSs), each with 10 units to measure the severity of the 5 major symptoms: fatigue, spinal pain, peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration) over the last week. To give each symptom equal weighting, the average of the 2 scores relating to morning stiffness is taken. The resulting 0 to 50 sum score is divided by 5 to give a final BASDAI score between 0 and 10, with lower scores indicating lower disease activity.

If 1 of the 2 morning stiffness measurements (ie, questions: [redacted]” and “[redacted]”) is missing, the other one will be used for the morning stiffness calculation. The same imputation is also applied for the calculation of the ASAS inflammation component, which is calculated as the average of the 2 morning stiffness measurements.

If 1 major symptom of the BASDAI is missing, the sum score of the remaining symptoms will be divided by the number of symptoms assessed. If more than 1 major symptom is missing, the sum score will be set to missing.

The BASDAI50 response is defined as an improvement of at least 50% in the BASDAI compared to Baseline.

Change from Baseline in BASDAI at Week 12 and Week 52 are secondary efficacy endpoints.

8.2.1.3 Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI contains 10 questions. The first 8 questions evaluate activities related to functional anatomical limitations due to the course of this inflammatory disease. The final 2 questions evaluate the subjects' ability to cope with everyday life. An NRS ranging from 0 to 10 is used to answer the questions on the test.

The mean of the 10 scales gives the BASFI score, which is a value between 0 and 10.

In case of missing answers to 1 or 2 of the single items within the BASFI questionnaire, the BASFI score will be calculated by imputing missing items with the mean of the completed items. Then, the BASFI score will be calculated as described above. If more than 2 of the items are missing, the BASFI score will be left missing.

Change from Baseline in BASFI at Week 12 and Week 52 are secondary efficacy endpoints.

8.2.1.4 Magnetic Resonance Imaging (MRI) assessments

The SPARCC scoring method for lesions found on the MRI is based on an abnormal increased signal on the short-tau-inversion recovery (STIR) sequence, representing bone marrow edema (defined as an increased signal in bone marrow on a T2-weighted sequence, reflecting an increased concentration of "free water" related to a bone lesion). Each SI joint is divided into 4 quadrants: upper iliac, lower iliac, upper sacral, and lower sacral. The presence of increased signal on STIR in each of these 4 quadrants is scored on a dichotomous basis, where 1 = increased signal and 0 = normal signal. Joints that include a lesion exhibiting intense signal are each given an additional score of 1 per slice that demonstrated this feature. Similarly, each joint that included a lesion demonstrating continuous increased signal of depth greater or equal 1 cm from the articular surface is also given an additional score of 1. The scoring is repeated in each of 6 consecutive coronal slices. Total SI joint SPARCC scores can range from 0 to 72.

The Berlin modification of the ASspiMRI-a is a scoring system with a concentration on STIR sequences without other fat saturation techniques. This scoring method quantifies active changes in 23 vertebral units (VU) of the spine (from C2 to S1). A VU is defined as the region between 2 virtual lines through the middle of each vertebra. Active inflammation is scored by grading the degree of bone marrow edema from 0 to 3 in 1 dimension on 1 or more consecutive slices that represent the highest level of inflammation in a particular VU. Total spine ASspiMRI-a score in the Berlin modification can range from 0 to 69.

The following imputation rules should be used for calculating the total for both SI joint SPARCC scores and spine ASspiMRI-a score in the Berlin modification:

- If all scores are NA at a visit, the imputed total is blank for that visit.
- Treat NA as 0 when computing the total score.
- Carry the NA score from the Baseline visit forward to all follow-up visits unless all scores at Baseline are NA.

- Carry the numeric score from the last visit with non-NA score forward if a score is NA at a follow-up visit (unless all scores are NA at follow-up).
- If ALL the Baseline scores are NA, then do not carry forward the baseline scores. Treat the subsequent visit as a surrogate Baseline.

The details related to how the MRI data will be read and adjudicated will be outlined in a separate imaging charter.

All Baseline values should be collected prior to randomization as MRI is required to be randomized into the study.

For post-Baseline visits, a time window of 2 weeks before or after the scheduled visit will be used for mapping MRI data to the given visit.

MRI data at Week 12 will be summarized based on the observed data after incorporating the appropriate visit window definitions. The summary of MRI data at Week 52 will use MMRM (see Section 4.2).

The change from Baseline in SIJ SPARCC score at Week 12 is a secondary efficacy endpoint.

8.2.1.5 Relevant changes to background medication

For purposes of this secondary efficacy variable, relevant changes to background medication will be defined as the following:

- The addition of a new DMARD or the change from one DMARD to another
- The addition of an NSAID or the change from one NSAID to another
- Increased dose of chronic oral corticosteroids
- Increased dose in chronic analgesic medications or the addition of a chronic analgesic medication

The variable to be measured is the number of subjects without relevant changes to background medications. Therefore, a subject who does not have any of the above relevant changes made to background medication during the study through Week 52 will be considered to have met this endpoint. Conversely, subjects who have one of the above relevant background medication changes or who do not complete the study to Week 52 will be considered as not having met this endpoint.

8.3 Analysis of other efficacy variables

Treatment group comparisons for CZP 200mg Q2W vs placebo will be performed based on the change from Baseline in other selected efficacy variables. These analyses will be performed using an ANCOVA model including Baseline score, treatment group, region, and MRI/CRP classification. The treatment differences and corresponding 95% CIs will be calculated based on the adjusted means. Missing values will be imputed using LOCF. The change from Baseline in the following variables will be analyzed in this manner:

- PGADA
- Morning stiffness (average of BASDAI questions 5 and 6)
- SF-36, PCS, MCS, and individual domains

- Fatigue NRS
- ASQoL
- Sleep Problems Index II domains of the MOS Sleep scale

Such analyses will also be done for the following continuous variables: BASDAI, BASFI, BASMI, total and nocturnal spinal pain (NRS), and MRI variables for time points not specified in the secondary efficacy analyses using the same analysis methods described in Section 8.2.1. (Note that the analyses of MRI variables will be based on all subjects and the subjects that are MRI+ at Baseline.) Additionally, ASDAS and ASAS response variables will be analyzed using a logistic regression model similar to the one specified for the primary analysis at time points not covered in the primary and secondary efficacy analyses. These comparisons are not part of the multiplicity-controlled testing procedure described in Section 8. The p-values reported for these analyses will not be adjusted for multiplicity and will be considered nominal.

For the 'resource utilization' variables 'number of concomitant medical procedures', 'number of health care provider consultations not foreseen by the protocol', 'number of hospitalizations', and 'number of emergency room visits' descriptive statistics and frequency distributions will be presented for the entire double blind period.

The treatment comparisons between groups for the WPS scores (Q2 to Q9) will be performed using the nonparametric bootstrap-t-method (see Appendix 13.1). Bootstrap confidence intervals and p-values will be provided. The analysis will be based on the FAS and will employ LOCF for the individual questions. The WPS [redacted] (Q1) will not be subject to exploratory statistical testing, and only descriptive statistics will be provided and presented for the FAS over time. For subjects who have missing data for [redacted] (Q1), the "missing" category will be used for display at the respective visit. WPS Q2 to Q4 will be analyzed for employed subjects in the FAS, whereas WPS Q5 to Q9 will be analyzed in the entire FAS.

Tables for continuous variables will display descriptive statistics for the time point itself and for the change from Baseline. This will be done for the FAS using observed case (OC) data and with imputation using last observation carried forward (LOCF).

Tables for the binary variables will display the responder rates for the various time points. As with the continuous variables, this will be presented in 2 ways. First, the responder rates will be presented for the FAS using OC data, where the denominator will be based on the number of observed values at the given time point. Second, they will be presented where the denominator is all subjects in the FAS for the given treatment group. This is essentially a non-responder imputation (NRI) approach as subjects who have not achieved the given outcome (whether observed or not) are treated as not having responded.

8.3.1 Derivation of other efficacy variables

Derivations of other efficacy variables not covered among the previous derivations are provided below.

8.3.1.1 Bath Ankylosing Spondylitis Metrology Index (BASMI)

The BASMI characterizes the spinal mobility of a subject with AS and consists of 5 clinical measures to reflect axial status: cervical rotation; tragus to wall distance; lateral spinal flexion; lumbar flexion (modified Schober); intermalleolar distance. Each of the 5 movements is scored

according the linear BASMI definition (see table below). The mean of the 5 scores provides the BASMI score. The higher the BASMI score the more severe the patient's limitation of movement due to their AxSpA.

BASMI linear definition

S = (21.1 cm –A) / 2.1 cm	For the lateral lumbar spine flexion (mean right/left)
S = (A – 8 cm) / 3 cm	For the tragus-to-wall distance (mean right/left)
S = (7.4 cm – A) /0.7 cm	For the lumbar flexion (modified Schober)
S = (124.5 cm – A) / 10 cm	For the maximal intermalleolar distance
S = (89.3° - A) / 8.5°	For the cervical spine rotation (mean right/left)
Always with the additional condition $0 \leq S \leq 10$	

S = score, A = assessment

For cervical rotation, tragus-to-wall distance and lumbar flexion, take the mean of the left and right measurements, if both are available. Otherwise, the available measurement will be used.

For the lumbar flexion (modified Schober), values greater than 9.0 cm (Maksymowych 2006) will be flagged as invalid and treated as if they were missing values. The below imputation rules apply for BASMI.

If 1 or 2 clinical measures for the BASMI are missing at one visit, the missing measure will be imputed by carrying the last observation forward, and the BASMI will be calculated accordingly. In no value is available for the clinical measure before the missing time point, the next observation may be carried backwards. If more than 2 items are missing, the BASMI score will be treated as missing.

8.3.1.2 Total and nocturnal spinal pain

Total and nocturnal spinal pain will be recorded based on a numeric rating scale (NRS) ranging from 0 to 10, where 0 represents no pain and 10 represents most severe pain.

8.3.1.3 Tender and Swollen Joint Counts (44 joints evaluation)

Tender and swollen joint counts will be carried out on the following 44 joints:

- Upper body (4) – bilateral sternoclavicular and acromioclavicular joints
- Upper extremity (26) – bilateral shoulders, elbows, wrists (includes radiocarpal, carpal and carpometacarpal bones considered as a single unit), metacarpophalangeals (MCPs) I, II, III, IV, and V, and thumb interphalangeals (IPs), and proximal IPs (PIPs) II, III, IV, and V
- Lower extremity (14) – bilateral knees, ankles, and metatarsophalangeals (I, II, III, IV, and V)

The assessment for swelling and tenderness is made on 44 joints from the above list. Artificial, ankylosed, and missing joints are excluded from swelling and tenderness assessments.

Each joint is scored as follows:

0 = None (not tender)

1 = Positive (tender)

TJC is the sum of tender joints among the 44 joints. It ranges from 0 to 44.

For swelling 44 joints will be assessed, which are the same as the list of joints for tenderness. Artificial, ankylosed, or missing joints will not be assessed.

Each joint is scored as follows:

0 = None

1 = Detectable

TJC and SJC are calculated as the sum of tender and swollen joints, respectively, among the 44 joints. It ranges from 0 to 44.

If there are missing observations for tender or swollen joints then the remaining observations will be assessed and weighted by dividing by number of non-missing and then multiplying by 44 for the joint count. If a joint is not evaluable at Baseline, then that joint is set to missing throughout the study.

If data for more than 50% of the joints are missing at the time of a given assessment, then no imputation will be done and the total TJC or SJC will be set to missing for that visit.

TJC summaries will be based only on those subjects with at least one tender joint at Baseline. Similarly, SJC tables will be based only on those subjects with at least one swollen joint at Baseline.

8.3.1.4 Patient's Global Assessment of Disease Activity (PGADA)

PGADA will be recorded based on an NRS describing how active the patient's spondylitis was on average over the past week. The range of the scale is from 0 to 10, where 0 represents not active and 10 represents very active.

8.3.1.5 Physician's Global Assessment of Disease Activity (PhGADA)

PhGADA is recorded by the physician on a visual analog scale (VAS) ranging from 0 to 100, where 0 is "very good, asymptomatic and no limitation of normal activities" and 100 is "very poor, very severe symptoms which are intolerable and inability to carry out all normal activities."

8.3.1.6 C-reactive protein (CRP)

Values of CRP below the lower limit of quantification (LLOQ) will be imputed as the midpoint between 0 and the LLOQ.

8.3.1.7 Spinal mobility

The following spinal mobility assessments will be performed in addition to those performed for the BASMI:

- Occiput to wall distance
- Chest expansion

8.3.1.8 Enthesitis (MASES)

The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) comprises 13 items (bilateral costochondral 1, costochondral 7, anterior superior iliac spine, posterior iliac spine, iliac crest

and proximal insertion of the achilles tendon sites, and the fifth lumbar vertebral body spinous process) (Heuft-Dorenbosch et al, 2003) each scored as 0 = yes or 1 = no and then summed for a possible score of 0 to 13, with higher scores indicating worse enthesitis.

If 7 or more items are available, MASES will be imputed by dividing the sum score with the number of assessments and multiplying the result with 13. If less than 7 times are available, MASES will be treated as missing.

Summaries of MASES will be restricted to the subset of subjects with enthesitis present at Baseline. Presence of enthesitis at Baseline will be defined as a Baseline MASES score >0.

8.3.1.9 Short-Form 36-item Health Survey (SF-36)

The SF-36 (Version 2, standard recall) is a 36 item generic HRQoL instrument that uses a recall period of 4 weeks. Items are grouped into 8 domains as follows: Physical Functioning (10 items), Role Physical (4 items), Bodily Pain (2 items), General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role Emotional (3 items), Mental Health (5 items), and a further unscaled single item (Q2) for perceived stability or change in health (Health Transition) during the last year. The concepts represented by these domains contribute to physical, mental, and social aspects of HRQoL.

The SF–36 domains (subscores) are scored so that a higher score indicates a better health state.

The norm-based scores (based on the US general population) will be utilized for analysis.

When calculating the SF-36 domain scores, the items will first be recoded according to the author's recommendations (Ware et al, 2007).

Item 1 is recoded as shown in the table below:

Item 1 – Response choices	Precoded value	Final recoded value
Excellent	1	5.0
Very good	2	4.4
Good	3	3.4
Fair	4	2.0
Poor	5	1.0

The score for items (and sub-items) 2, 3, 4, and 5 are not recoded. Items 2, 4, and 5 have a score range of 1-5. Item 3 has a score range of 1-3.

Item 6 is recoded according to the table below:

Item 6 – Response choices	Precoded value	Final recoded value
Not at all	1	5
Slightly	2	4
Moderately	3	3
Quite a bit	4	2
Extremely	5	1

Item 7 is recoded according to the table below:

Item 7 – Response choices	Precoded value	Final recoded value
None	1	6.0

Very mild	2	5.4
Mild	3	4.2
Moderate	4	3.1
Severe	5	2.2
Very Severe	6	1.0

Item 8 is recoded depending on whether item 7 is answered or not, according to the table below:

Scoring of item 8 <u>if both</u> items 7 and 8 are answered			
Item 8 – Response choices	**Item 8 – Precoded value**	**Item 7 – precoded value**	**Item 8 – Final recoded value**
Not at all	1	1	6
Not at all	1	2 through 6	5
A little bit	2	1 through 6	4
Moderately	3	1 through 6	3
Quite a bit	4	1 through 6	2
Extremely	5	1 through 6	1
Scoring of item 8 if item 7 is not answered			
Not at all	1	NA	6.0
A little bit	2	NA	4.75
Moderately	3	NA	3.5
Quite a bit	4	NA	2.25
Extremely	5	NA	1.0

Items 9b, 9c, 9f, 9g, and 9i are not recoded and have a range of 1-5. However, items 9a, 9d, 9e, and 9h are recoded according to the table below:

Items 9a, 9d, 9e, and 9h – Response choices	**Precoded value**	**Final recoded value**
All of the time	1	5
Most of the time	2	4
Some of the time	3	3
A little of the time	4	2
None of the time	5	1

Item 10 is not recoded and has a range of 1-5.

Item 11a and 11c are not recoded and have a range of 1-5. However, items 11b and 11d are recorded according to the table below:

Item 11b and 11d - Response choices	Precoded value	Final recoded value
Definitely true	1	5
Mostly true	2	4
Don't know	3	3
Mostly false	4	2
Definitely False	5	1

A sub-scale score per domain is calculated as follows:

Physical Functioning (PF) =3a+3b+3c+3d+3e+3f+3g+3h+3i+3j

Role Physical (RP) =4a+4b+4c+4d

Bodily pain (BP) =7+8

General health (GH) =1+11a+11b+11c+11d

Vitality (VT) =9a+9e+9g+9i

Social Functioning (SF) =6+10

Role Emotional (RE) =5a+5b+5c

Mental health (MH) =9b+9c+9d+9f+9h

There is a further unscaled single item (Q2) asking respondents about health change over the past year.

SF-36 sub-scales are scored so that a higher score indicates a better health state.

A simple mean imputation of missing data with a restriction to cases where the respondent has completed at least 50% of the items of that scale (the "half-scale" rule) will be used.

The raw domain scores will be transformed on a 0–100 scale (transformed domain scores) and then standardized into norm-based scores:

Transformed domain score = 100 x (Actual raw score – lowest possible raw score) / (Possible raw score range)

Each transformed domain score is standardized using a z-score transformation and the following formulas:

PF_Z = (PF – 83.29094) / 23.75883

RP_Z = (RP – 82.50964) / 25.52028

BP_Z = (BP – 71.32527) / 23.66224

GH_Z = (GH – 70.84570) / 20.97821

VT_Z = (VT – 58.31411 / 20.01923

SF_Z = (SF – 84.30250) / 22.91921

RE_Z = (RE – 87.39733) / 21.43778

MH_Z = (MH – 74.98685) / 17.75604

The next step is the transformation of each z-score to a norm-based score using a t-score transformation (Mean=50, SD=10) and the following formulas:

Norm-based PF = 50 + (PF_Z * 10)

Norm-based RP = 50 + (RP_Z * 10)

Norm-based BP = 50 + (BP_Z * 10)

Norm-based GH = 50 + (GH_Z * 10)

Norm-based VT = 50 + (VT_Z * 10)

Norm-based SF = 50 + (SF_Z * 10)

Norm-based RE = 50 + (RE_Z * 10)

Norm-based MH = 50 + (MH_Z * 10)

Following the transformation of the eight domain scores into z-scores, the Mental Component Summary (MCS) and the Physical Component Summary (PCS) are aggregated using weights from the 1990 US general population:

AGG_PHYS = (PF_Z * 0.42402) + (RP_Z * 0.35119) + (BP_Z * 0.31754) + (GH_Z * 0.24954) + (VT_Z * 0.02877) + (SF_Z * -0.00753) + (RE_Z * -0.19206) + (MH_Z * - 0.22069)

AGG_MENT = (PF_Z * -0.22999) + (RP_Z * -0.12329) + (BP_Z * -0.09731) + (GH_Z * -0.01571) + (VT_Z * 0.23534) + (SF_Z * 0.26876) + (RE_Z * 0.43407) + (MH_Z * 0.48581)

Finally, each component score is transformed to norm-based scoring using the following formulas:

Transformed Physical (PCS) = 50 + (AGG_PHYS * 10)

Transformed Mental (MCS) = 50 + (AGG_MENT * 10)

Component scale scores (PCS and MCS) will be set to missing if the subject is missing any one of the eight SF-36 domain scales.

While the norm-based scores are calculated such that the mean ± SD of these scores in the US general population is 50 ± 10, the lowest and highest possible scores for the PCS are 1 and 81, respectively. For the MCS, the lowest and highest possible scores are -9 and 82, respectively.

8.3.1.10 ASAS-NSAID score

The ASAS-NSAID score is a tool that has been developed to measure the magnitude of NSAID intake during clinical studies (Dougados et al, 2011). In order to calculate the ASAS-NSAID score, the following information will be collected:

- Has there been NSAID intake since last visit?
- NSAID name
- Average daily intake (mg)
- Days with intake

  - <1 day/week
  - 1-3 days/week
  - 3-5 days/week
  - ≥5 days/week
  - Every day
- Starting date
- End date (or ongoing)

The general formula for the calculation is as follows:

- (equivalent NSAID score) × (days of intake during period of interest) × (days per week)/(period of interest in days)

Each of the components of the above calculation are described below:

- Equivalent NSAID score: This is reported in terms of NSAID equivalent dose in mg/day on a 0–100 scale where the 150mg equivalent diclofenac is set to 100. An NSAID equivalence table was developed based on a survey of ASAS members. The table including the consensus equivalence score for various NSAIDs can be found in Appendix 13.3.
- Days of intake during period of interest: Equivalent to the total number of days covered during the period that is being measured.
- Days per week: Number of days per week when the NSAID is taken. This is collected in the categories described in the days with intake category listed above. Each category corresponds to a score as follows (score in parentheses):
  - Every day (7)
  - ≥5 days/week (6)
  - 3-5 days/week (4)
  - 1-3 days/week (2)
  - <1 day/week (0.5)
  - No NSAID intake (0)
- Period of interest in days: Refers to the number of days covered for a given NSAID. If only 1 NSAID was taken during the period of interest, this will be the same as days of intake during period of interest.

Dougados, et al provide the following example. If during a period of interest (between two visits) of 6 months, the patient has taken piroxicam 20mg during 4 months and if during this 4-month period he has taken piroxicam 3–5 days per week the calculation is as follows:

- 100 (20mg piroxicam score) × 120 (4 months) × 4/7 (3–5 days/week)/180 (6 months) = 38.1

If the patient has used 10mg piroxicam during the remaining 2 months on 2 days a week, the NSAID score for this period is:

- 50 (10 mg piroxicam score) ×60 (2 months) × 2/7 (1–3 days/week)/180 (6 months) = 4.8

In this example the total score for the 6 month period is 42.9 (38.1 plus 4.8).

8.3.1.11 Ankylosing Spondylitis Quality of Life (ASQoL)

The ASQoL consists of 18 items, each with a score of 0 = no or 1 = yes, so that the sum score ranges from 0 to 18, with higher scores indicating worse quality of life.

If 6 or fewer items are missing, the missing responses will be imputed with the mean of the available responses from that visit to calculate a total score. If more than 6 items are missing, the total score will be left missing.

8.3.1.12 Work Productivity Survey (WPS)

The WPS is a 9 question instrument used to assess the impact of arthritis on productivity within and outside the home during the preceding 4 weeks. [redacted] on a 0 to 10 scale (0=no interference; 10=complete interference), [redacted] on a 0 to 10 scale (0=no interference; 10=complete interference).

In order to make data consistent and amenable to statistical analysis, the following counting rules will be applied to handle out of range and ambiguous answers of the WPS.

These counting rules will be applied prior to conducting any type of statistical analysis of the data. Of note, these counting rules do not represent imputation methods for missing data applied during the statistical analysis (ie, LOCF). These rules will be described further down in this section.

WPS counting rules

Due to the inter-relation between certain questions of the WPS, the priority order for implementing these specific counting rules is as in the listed order below.

WPS Question 1 (Q1) ([redacted])

- If (Q1=missing) and (Q2>0 or Q3>0 or Q4>0), then Q1=YES.
- If (Q1=missing) and {(Q1.a (1) is not missing) or (Q1.a (2) is not missing)}, then
- Q1=YES.
- If (Q1=missing) and (Q1.b is not missing), then Q1=NO.

For all rules below, the original value will be kept and displayed in the listings but the corrected value will be considered for the analyses (tables).

– If [redacted]="No" and Job function is not " " then Job function=" ".

- If [redacted]="No" and occupation is not " " then Job occupation=" ".
- If [redacted]="Yes" and patient's status is not " " then status=" ".

WPS Q2 ([redacted])

- If (Q1=NO), then Q2="." (missing)
- If Q2 =0 or missing (.) and if Q1 ([redacted]) is Missing (.) then Q2=. (replace 0 by ".").

WPS Q3 ([redacted])

- If (Q1=NO), then Q3="." (missing).
- If Q3 =0 or missing (.) and if Q1 ([redacted]) is Missing (.) then Q3=. (replace 0 by ".").

WPS Q4 ([redacted]

- If (Q1=NO), then Q4="." (missing).
- If Q4 is out of range, then Q4="." (missing).
- If Q4=0 or missing (.) and if Q1 ([redacted]) is Missing (.) then Q4=. (replace 0 by ".").

WPS Q9 ([redacted])

- If Q9 is out of range, then Q9="." (missing).

WPS Q2 to Q9

For the rule below, the original value will be kept and displayed in the listings but the corrected value will be considered for the analyses (tables).

- If value=X.5 then value=X+1 (for ex: 1.5->2).

With regards to missing observations at Baseline, the following rules apply:

- Q1 (categorical): missing Baseline is not imputed

Q2-Q9 (discrete): missing Baseline is imputed by the mean of the available subjects, rounded to the closest integer.

For WPS, in general the same rules as for other efficacy variables have to be applied for the LOCF imputation. In case of discrepancies in the LOCF data, the following correction rules have to be applied for Q1, Q2, Q3 and Q4 prior to any analysis of the data to make the data consistent and amenable to statistical analysis:

If Q1='No' and Job function is not ' ' then Job function=' '.

If Q1='No' and occupation is not ' ' then Job occupation=' '.

If Q1='Yes' and patient's status is not ' ' then status=' '.

If Q1='No' and Q2 is not missing, then Q2='.'

If Q1='No' and Q3 is not missing, then Q3='.'

If Q1='No' and Q4 is not missing, then Q4='.'

8.3.1.13 Medical Outcomes Study (MOS) sleep scale

The MOS Sleep Scale is a validated generic self-administered scale measuring specific aspects of sleep. The frequency with which each problem has been experienced during the previous 4 weeks is rated on a 6-point scale ranging from "none of the time" to "all of the time", except sleep quantity, which is reported in hours. All scores are transformed linearly to range from 0 to 100, again with the exception of the sleep quantity subscale, which is scored in hours. Higher scores indicate more of the attribute implied by the scale name (eg, more sleep disturbance, more adequate sleep, or greater sleep quantity).

The item scores (1, and 3 through 12) are used to derive 7 different scale scores. In addition, the [redacted] (Item 2) is used to create a raw and a dichotomized measure of sleep. The scale scores are created by averaging the respective rescaled item scores. Scales with at least 1 item answered can be used to generate a scale score. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Scores represent the average for all items in the scale that the respondent answered. The table below describes which items are used for each sleep scale.

MOS Sleep Scale Scores

Scale (short name)	Scale (description)	Number of items	Item scores
SLPD4	Sleep disturbance	4	1, 3 (R), 7 (R), 8 (R)
SLPSNR1	Snoring	1	10 (R)
SLPSOB1	Sleep short of breath or headache	1	5 (R)
SLPA2	Sleep adequacy	2	4 (R), 12 (R)
SLPS3	Sleep somnolence	3	6 (R), 9 (R), 11 (R)
SLP6	Sleep problems Index I	6	4, 5 (R), 7 (R), 8 (R), 9 (R), 12
SLP9	Sleep problems Index II	9	1, 3 (R), 4, 5 (R), 6 (R), 7 (R), 8 (R), 9 (R), 12

Note: (R) refers to a reversed item.

Prior to averaging, the item score is re-scaled as shown in the following table.

MOS Sleep Scale recoding of items

Item numbers	Original response category	Re-coded value (not reversed)	Re-coded value (reversed)
1	<1	.	-- N/A --
	1	0	
	2	25	
	3	50	
	4	75	
	5	100	
	>5	.	

3, 5, 6, 7, 8, 9, 10, 11	<1 1 2 3 4 5 6 >6	-- N/A --	. 100 80 60 40 20 0 .
4, 12	<1 1 2 3 4 5 6 >6	. 0 20 40 60 80 100 .	. 100 80 60 40 20 0 .

N/A=not applicable.

In addition, [redacted] (Item 2) is used to create a raw and a dichotomized measure of sleep and is referred to as the Sleep Quantity raw score (SLPQRAW). This variable is further dichotomized and referred to as Optimal Sleep (SLPOP1) and takes the value 0 (non-optimal sleep) or 1 (optimal sleep). The dichotomization is defined in the following table.

MOS Sleep Scale: Optimal Sleep Dichotomy

MOS Item Score 2 (MOS2)	SLPOP1
< 1	. (out-of-range)
1 – 6	0
7 – 8	1
9 – 23	0
24+	. (out-of-range)

Non-integer recorded values for sleep will be rounded to the nearest integer prior to dichotomization for the SLPOP1 variable.

The domains of interest for this study are the Sleep Disturbance and the Sleep Problems Index II domains.

8.3.1.14 Health Status (EQ-5D)

The EQ-5D consists of a 5-item health status measure and a visual analog rating scale (VAS). Each of the 5 health states is divided into 3 levels (no problem, some or moderate problems, and extreme problems) and is scored as 1, 2, and 3, respectively. The EQ-5D VAS records the respondent's self-rated health status on a vertical 20cm scale, 0 to 100 graduated (0=worst imaginable health status, 100=best imaginable health status).

The VAS will be evaluated by changes from baseline and actual scores. The 5 dimensions will be analyzed categorically.

If electronic data capture is being used, ambiguous and out of range answers are not expected. However, if these rules are needed, see Appendix 13.2.

8.3.1.15 Resources Utilization

The following resource utilization data were collected through UCB standardized modules:

- In–patient hospitalization and emergency room visits
- Health care provider consultations not foreseen by the protocol
- Concurrent medical procedures

Summary statistics and frequency distribution (number of subjects by number of medical resources used) will be presented based on the entire study period for concurrent medical procedures, health care provider consultations, hospital visits and emergency room (ER) visits. ER visits will be extracted from the hospitalizations/emergency room visit CRF page (if initial entry point emergency room is ticked).

The categories to be displayed for the frequency distributions of the resource use variables will be defined at a later stage depending on the data.

A medical resource is allocated only once in its period of onset, as determined by the (start) date of the event. A resource will be attributed in the same way as an AE is considered a TEAE. The same rules for (partially) missing start and end dates as for AEs will be applied for the resource use..

For the same subject only one hospitalization will be considered if "start date of the second hospitalization - end date of the first hospitalization ≤ 1".

In case of complete consultation date, count only once for a same subject, same consultation date, same location and same provider.

If the procedure name, start date and relationship are the same, then only one procedure is counted, otherwise if at least one variable among procedure name, start date or relationship is different, distinct/several procedures are counted.

If concomitant medical procedures, health care provider consultations not foreseen by the protocol, and hospitalizations/emergency room visits are not available during the study, the respective number variable will be set to 0.

8.3.1.16 Extra-articular assessments

The evolution of associated nonmusculoskeletal features including inflammatory bowel disease, psoriasis, uveitis (including their severity), and flare rate history will be assessed.

9 PHARMACOKINETICS , PHARMACODYNAMICS, AND PHARMACOGENOMICS

9.1 Pharmacokinetics

Certolizumab pegol plasma concentration data will be tabulated and summarized by treatment group (overall and by antibody status within each treatment group) for each visit at which

samples were taken for the SS. Geometric mean, geometric coefficient of variation (CV), 95% CIs, arithmetic mean, arithmetic SD, minimum, and maximum, will be presented. For each treatment group, plasma concentration time curves will be plotted overall and by antibody status.

The value of blood sample measurements that are deemed to be below the level of quantification (BLQ), will be set to half the lower level of quantification (LLOQ) for analysis purposes. The summary statistics will only be displayed if at least two-thirds of the values are above the LLOQ.

9.2 Pharmacodynamics

Not applicable.

9.3 Pharmacogenomics

Pharmacogenomic variables that are selected for analysis (see Section 2.2.2.2) will be summarized descriptively by visit.

10 IMMUNOLOGICAL PROCEDURES

Frequency tables of anti-CZP antibody (ADAb) status by visit will be presented for the SS.

The number and percentage of subjects with anti-CZP antibody concentrations above 2.4 units/mL will be reported as follows:

- Number and percentage of subjects with ADAb >2.4 units/mL at the time of each visit
- Number and percentage of subjects with ADAb >2.4 units/mL at any visit during treatment (not including post treatment withdrawal or follow up visits)
- Number and percentage of subjects with ADAb >2.4 units/mL at any visit including post treatment withdrawal or follow up visits.

For the subgroup of subjects with at least 1 anti-CZP antibody level above 2.4 units/mL, the time point of occurrence of the first finding will also be displayed.

11 SAFETY ANALYSES

The SS will be utilized for safety analyses.

Laboratory evaluations and vital signs will be analyzed over time in the SS for observed cases and at the end of treatment.

11.1 Extent of exposure

There are 4 different concepts for calculating exposure.

1. This approach will look at the number of doses received, which is defined as dosing days.

2. For the CZP 200mg and placebo treatment arms, duration of exposure to study medication will be calculated as:

Date of last administration of CZP 200mg or placebo study medication – date of first administration of CZP 200mg or placebo study medication + 14 days (14 days are included in this definition as this is the dosing interval for maintenance of subjects).

If a subject dies during the exposure period (first injection to last injection + 14 days), the exposure period will end with the death date.

For subjects discontinuing from the study before Week 52, the 2-week period after last double-blind injection will be utilized.

3. For the study exposure of a subject, 5 half-lives of CZP will be taken into account. Hence, a subject will be regarded as being exposed to study drug from first injection to last injection + 70 days. The days of drug holidays beyond 70 days will be subtracted.

If a subject dies during the exposure period (1st injection to last injection + 70 days), the exposure period will end with the death date.

For subjects discontinuing from the study before Week 52, the 70 day period after last injection will be utilized.

4. This approach will be the nearly identical to approach 2. However, exposure will be censored at the first occurrence of the AE to be considered for analysis (a separate calculation has to be performed for each preferred term). The different exposure duration for the respective AEs will only be displayed in the AE tables for exposure-adjusted incidences and will not be summarized in the exposure table.

For the first 3 approaches, tables will summarize exposure days for the placebo treatment group and the CZP 200mg Q2W group.

11.2 Adverse events

A treatment-emergent AE (TEAE) is defined as an AE occurring after first study drug administration until last study drug administration + 70 days. AEs recorded on the Baseline day will be regarded as 'treatment-emergent'. If a subject dies during the treatment period (1st injection to last injection + 70 days) the period for TEAEs will end with the death date. For subjects early terminating before Week 52, the 70 day period after last injection will be utilized.

AEs occurring either before study drug administration (pre-treatment) or after a 70-day period after drug administration (this includes treatment gaps of more than 70 days) will be defined as non-treatment emergent. Non-treatment emergent AEs (those occurring in the pre-treatment period and after the 70 day post-treatment period) will be presented in a listing.

If AE intensity or relationship is missing, then the given event will be imputed as severe or related, respectively.

The frequency of all AEs including TEAEs will be presented for each treatment group separately by System Organ Class, high level term, and preferred term. The data will be displayed as number of subjects experiencing the AEs, percentage of subjects, and number of AEs. Certain summaries will also include exposure-adjusted incidence rates and event rates.

The following AE summaries will be presented:

- Overview of TEAE
- TEAE
- Serious TEAE
- Non-serious TEAE
- TEAE with fatal outcome

- TEAE leading to permanent withdrawal of study medication
- Severe TEAE (included in TEAE table by intensity)
- Drug-related TEAE (included in TEAE table by relationship)
- Serious TEAE by relationship
- Non-serious TEAE by relationship
- Fatal TEAE by relationship
- Injection reactions (Injection site reactions, systemic injection reactions, acute systemic injection reactions, and delayed systemic injection reactions)
- TEAE of special interest (see below)
- TEAE sorted by incidence of PTs in the CZP 200mg group (SOC and HLT will not be utilized)
- Non-serious TEAE with an incidence of at least 5% in 1 of the 2 randomized groups (HLT will not be utilized)
- Non-serious TEAE with an incidence of at least 5% in 1 of the 2 randomized groups by relationship (HLT will not be utilized)
- TEAE subject numbers

The AEs of interest and the approach for summarizing them are described below:

1. Serious infections, including opportunistic infections. Serious infections will be summarized using the Serious TEAE table. No separate table is planned. In addition, opportunistic infections (including tuberculosis) will be presented in a table using UCB-defined search criteria.
2. Malignancies, including lymphoma. These will be presented in 2 tables using the criteria SMQ = “Malignant or unspecified tumours” and SMQ=”Malignant tumoursMalignancies”, respectively.
3. Congestive heart failure. These will be manually identified by the study physician from the TEAE table. No separate table is planned. In addition, major adverse cardiac events (MACE) will be presented in a table using UCB-defined search criteria and will include fatal and serious non-fatal myocardial infarction, cerebrovascular events and congestive heart failure.
4. Demyelinating-like disorders. These will be manually identified by the study physician from the previously described TEAE table. No separate table is planned.
5. Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia. These will be presented in a table using the criteria SMQ = “Haematopoietic cytopenias” in the subset of SAEs.
6. Serious bleeding events. These will be presented in a table using the criteria SMQ = “Haemorrhages” in the subset of SAEs.

7. Lupus and lupus-like illness. These will be manually identified by the study physician from the TEAE table. No separate table is planned.
8. Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, anderythema multiforme). These will be manually identified by the study physician from Serious TEAE table. No separate table is planned.

The tables for 1, 2, 3, 5, and 6 above will include the incidence rate with associated 95% confidence interval, and the exposure adjusted event rate.

Although not an AE of interest, hepatic events will also be summarized. They should be identified using the following 5 SMQs: Cholestasis and jaundice of hepatic origin; Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions; Hepatitis, noninfectious; Liver-related investigations, signs and symptoms; and Liver-related coagulation and bleeding disturbances.

Because subjects will be able to adjust background medications during the study, some additional AE tables will be prepared in which events occurring while on certain background medications will be summarized. The list of these supportive tables is as follows:

- TEAEs reported after starting a new biologic, but within 10 weeks of stopping CZP
- TEAEs reported one month after changing NSAID type
- TEAEs reported three months after changing or adding a DMARD
- TEAEs reported within one month of an addition of oral corticosteroids or 50% increase in dose

The purpose of these tables will be to assess whether any observed treatment differences in the AE profile may be due, in part, to these prespecified background medications.

A TEAE table will also be presented for the 'anti-CZP antibody status' subgroup. Only the subjects exposed to CZP will be considered and displayed by the antibody status (negative/positive). For this table, a subject is positive if at least 1 anti-CZP antibody level above 2.4 units/mL is observed at any time point during the study. A subject is negative if no anti-CZP antibody level above 2.4 units/mL is observed at any time point during the study. A further positive column will be presented by summarizing the TEAEs occurring after the onset of the positive antibody status.

The TEAE incidence rates will also be adjusted for exposure and reported by 100 patient-exposure years. Two approaches will be applied to adjust for exposure. One will only use the first occurrence of an AE with corresponding exposure (exposure-adjusted incidence rate [EAIR]) and the second approach will use all AEs and the entire exposure (exposure-adjusted event rate [EAER]).

For the exposure adjusted incidence rates, the first occurrence of an TEAEs for a certain treatment group will be utilized (either placebo or CZP 200mg) and divided by the sum of exposure of all subjects in the respective treatment group, where subjects experiencing the respective AE will be censored at the time of occurrence of the AE. The rates will be multiplied by a factor of 100 to give a rate per 100 patient-years.

For the exposure adjusted event rates, all TEAEs for a certain treatment group will be utilized (either placebo or CZP 200mg) and divided by the sum of exposure of all subjects in the respective treatment group. The rates will be multiplied by a factor of 100 to give a rate per 100 patient-years.

The summary of TEAEs, serious TEAEs, and TEAEs leading to permanent withdrawal of study medication will include the EAIR (with corresponding 95% exact CI) and EAER. The confidence interval for the EAIR will be based on the chi-square distribution (Ulm, 1990).

Date imputation for incomplete or missing start and/or stop dates

Where an AE start date is (partially) missing, the AE will be considered TE if possible.

The following rules are based on the assumption that if the start date is incomplete, either day only is missing, or day and months are missing, or date is completely missing.

Although the algorithms for treatment-emergence depend on the onset date, imputation rules are provided for resolution date as well, as these may be needed for certain statistical analyses, such as an analyses of AE prevalence or AE duration.

Imputation of Partial Onset Dates

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of onset, then use the 1st of the month
- If only the month and year are specified and the month and year of first dose is the same as the month and year of onset, then use the date/time of first dose
- If only the year is specified, and the year of first dose is not the same as the year of onset, then use January 1 of the year of onset
- If only the year is specified, and the year of first dose is the same as the year of onset, then use the date/time of first dose
- If the AE onset date is completely unknown, then use the date of first dose

Imputation of Partial Resolution Dates (if needed)

- If only the month and year are specified, then use the last day of the month
- If only the year is specified, then use December 31 of that year
- If the AE resolved and the resolution date is completely unknown, then do not impute the resolution date

If there are incomplete dates not covered by the rules above (eg, only month is missing and day and year are available), individual definitions will be made prior to unblinding.

Listings for TEAEs, serious TEAEs, TEAEs leading to withdrawal of study medication, and TEAEs with fatal outcome will be provided. Relative days in the listings will use imputed dates, whereas the date itself will be displayed with incomplete data, if present. A glossary for the reported terms will also be generated utilizing SOC, HLT, and PT.

11.3 Clinical laboratory evaluations

The changes from Baseline in laboratory evaluations will be analyzed over time in the SS for observed cases. In addition, last value (end of treatment), minimum value during treatment, and maximum value during treatment will be analyzed. End of treatment will be defined as last visit not including the Safety Follow-up visit. During treatment for the minimum and maximum calculation will also exclude the Safety Follow-up visit.

Shift tables concerning the normal range at end of treatment, minimum and maximum shift at any time will also be produced for each hematology and biochemistry laboratory parameter. The shifts will be categorized using L, N, H, missing, and total.

The number and percent of subjects with markedly abnormal (≥grade 3 by RCTC) hematology or biochemistry values will be summarized by visit and for any visit. Subject numbers for subjects with any markedly abnormal hematology or biochemistry value will be tabulated. Values fulfilling the criteria below will be classified as marked abnormal high (MH) or marked abnormal low (ML). If no lower (upper) limit is given, the classification ML (MH) is not applicable.

- Hemoglobin < LLN and decrease from Baseline >2g/dL
- Hemoglobin <8g/dL
- White blood cells <2000/µL
- Lymphocyte count <1000/µL
- Neutrophil count <1000/µL
- Platelet count <50000/µL
- ALT >3x upper limit normal (ULN)
- AST >3x ULN
- AP >3x ULN
- Bilirubin ≥2x ULN
- Creatinine >1.8x ULN
- Calcium >12.5mg/dL
- Calcium <7mg/dL
- CK >4x ULN
- Glucose >250mg/dL
- Glucose <40mg/dL
- Potassium >6.4mmol/L
- Potassium <3mmol/L
- Sodium <125mmol/L
- Uric acid ≥3x ULN

The marked abnormalities will also be derived for the Double-Blind Treatment Period (any visit), not including the Safety Follow-up visit.

The liver function test elevations will be displayed in an incidence table for the entire Double-Blind Treatment Period.

If a repeat sample is taken, the repeated sample data will be used when possible. If the value of a parameter collected at the scheduled visit is missing and an additional sample associated with this visit is taken before the next scheduled visit, the missing value will be replaced by this value. Early Withdrawal Visits will be assigned to what would have been the next scheduled visit.

In the Urinalysis, microscopy (WBC, RBC, casts, crystals, and bacteria) will be performed only when there are abnormalities on the dipstick. This data will be listed and not presented in tables.

11.4 Vital signs, physical findings, and other observations related to safety

11.4.1 Vital signs

The changes from Baseline in vital signs will be analyzed over time in the SS for observed cases. In addition the last value (end of treatment), minimum value during treatment, and maximum value during treatment will be analyzed. End of treatment will be defined as last visit not including the Safety Follow-up visit. During treatment for the minimum and maximum calculation will also exclude the Safety Follow-up visit.

Early Withdrawal Visits will be assigned to what would have been the next scheduled visit.

The number and percent of subjects with abnormal vital sign values will be summarized by visit and for any visit. Subject numbers for subjects with any abnormal value will be tabulated.

11.4.2 Electrocardiograms

Not applicable.

11.4.3 Other safety variables

11.4.3.1 Weight

The changes from Baseline in weight will be analyzed over time in the SS for observed cases and end of treatment, minimum value during treatment, and maximum value during treatment.

11.4.3.2 Pregnancy testing

Pregnancy testing will consist of serum testing at Screening and urine testing (dipstick) at all other applicable visits. Pregnancy testing must be carried out at Screening, Baseline, Week 52/Withdrawal, and at SFU. The Screening and Baseline tests will only be utilized to verify the eligibility criteria and the tests during study to check if a woman has to be withdrawn from the study. No tables will be generated and data will be listed only.

11.4.3.3 Physical assessments

Physical examination will be performed at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 24, 36, 52 and at the Safety Follow-Up Visit (10 weeks after the last dose). Physical examination findings will be recorded in the CRF only at Screening. Physical examination data will be listed only.

11.4.3.4 Tuberculosis assessments

The TB assessments at Screening will only be performed to verify the eligibility criteria (presence of active TB or new latent TB infection). These data will be presented as Baseline characteristics (see Section 6.2).

The TB assessments during the study will be utilized to check if a subject has to be withdrawn from the study. No tables will be generated and data will be listed only.

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13 APPENDICES

13.1 Non-Parametric bootstrap-t method

Barber and Thompson note (Barber and Thompson, 2000) that it is a common statistical problem in the analysis of cost data from clinical trials to provide comparisons and inferences regarding the total costs associated with each treatment group, in the presence of highly skewed cost distributions. Standard non-parametric tests (that compare the overall shape of distributions) or log transformation to normalize data (that compare geometric means) are not always suitable because for cost data the analysis needs to focus on the arithmetic mean costs rather than the overall differences in the shape of the distribution, the medians, or the geometric means. The relevance of the arithmetic mean is that it can be used to calculate the total costs of treatment, which is needed to inform health economic policy decision makers. The non-normality of cost distributions also means that standard parametric comparisons of means based on the normal distribution (ANOVA and two-sample t-tests) may not be suitable. In such cases, bootstrap techniques can be recommended when making inferences about arithmetic means for moderately sized samples of highly skewed data such as healthcare costs. The cost data approach will be applied to the WPS-RA.

A) Bootstrap Principle

The bootstrap is a data based simulation method that is useful for deriving confidence intervals and hypothesis testing when the sampling distribution of an estimator is not known or cannot be defined mathematically. A balanced bootstrap resampling method (Gleason, 1988) is used to increase the precision of the bootstrap bias and the SE, where each observation occurs a total of B times in the collection of B bootstrap samples. This does not force each bootstrap sample to contain all observations; the first observation may occur twice in the first bootstrap sample and not at all in the second, while the second observation may occur once in each sample.

Samples of the same size as originally observed are drawn separately from each treatment group by sampling with replacement from the observed data. For each resample, the statistic of interest (difference in means) is calculated. The distribution of these B (where B = number of bootstrap samples) values provides an approximation of its population sampling distribution and can be used to estimate confidence intervals and to conduct hypothesis tests. Typically, a large number of bootstrap resamples are calculated (10000 resamples in this analysis).

The bootstrap-t method involves generating bootstrap-t values which can be used in place of the standard t-distribution values to calculate confidence intervals and p-values.

Bootstrap resampling is used to obtain an approximation to the distribution of the test statistic under the null hypothesis of equal means. This distribution is then directly compared with the observed value of the test statistic to estimate the p-value. The most reliable test statistic for comparison of means is the studentized statistic, which is the difference in means divided by its standard error and will be calculated for each bootstrap resample as:

$$T_b^* = (M_b^* - M)/SE_b^*$$

where M_b^* is the difference in bootstrap means between treatment groups, M the observed difference in means between treatment groups, and SE_b^* the standard error of the bootstrap

difference in means between treatment groups. The standard error of the difference in means is calculated using the same method as for a t-test with unequal variances:

$$SE_b^* = \text{sqrt}\ [\ ((SD_{yb}^*)^2/m) + ((SD_{zb}^*)^2/n)\ ]$$

where SD_{yb}^* and SD_{zb}^* are the observed standard deviations of the bootstrap samples y_b^* and z_b^* in each treatment group (group y with sample size m and group z with sample size n).

Note that in some rare cases $SE_b^*=0$. When SE_b^* and $(M^* - M)$ are both equal to 0, then $T_b = (M_b - M)/SE_b$ is considered to be 0. When $SE_b = 0$ and $(M_b - M) \neq 0$, then $T_b = (M_b - M)/SE_b$ is considered to be tending towards infinity, and is therefore greater than t_{obs} in the p-value calculation described in Part B.

B) Bootstrap Hypothesis Test

The estimated distribution of the test statistic under the null hypothesis of no difference in means is used instead of a standard t-distribution to obtain the approximate two-sided p-value:

$$P\text{-value} \quad \hat{P}_{boot} = \#\{|t_b^*| \geq |t_{obs}|\} / B,$$

where t_{obs} is the observed value of the test statistics. If the distribution of bootstrap-t values is close to the standard t-distribution then the p-value from the usual t-test and that from the bootstrap-t will be similar.

It is recognized that the bootstrap-t test performs best on a variance-stabilized scale where the difference in means and its standard error are independent. This independence can be assessed from a plot of the bootstrap values (ie differences in means M_b^*) against their corresponding standard errors (SE_b^*). If there is a strong relationship between these, the test should be carried out after a variance stabilizing transformation.

The current analysis will be conducted after a variance stabilizing transformation of the bootstrap values. (*See Part D below*)

C) Bootstrap Confidence Intervals

To estimate a 100(1−α)per cent confidence interval, the 100(α/2)per cent and 100(1−α/2)per cent percentiles of T* ($T^*_{(\alpha/2)}$ and $T^*_{(1-\alpha/2)}$, respectively) are used.

For the estimation of a 100(1-α) per cent confidence interval for the difference in means, the confidence interval is given by:

$$(M - T^*_{(1-\alpha/2)}\, SE(M),\ M - T^*_{(\alpha/2)}\, SE(M))$$

where M is the observed difference in means and SE(M) its standard error.

The distribution of bootstrap-t values (T*) is obtained in the same way as previously described for hypothesis testing. The 100α percentile is estimated by the α(B+1)th member of the ordered bootstrap sample if this is a whole number; otherwise linear interpolation must be used (Davison and Hinkley, 1997).

As before for the bootstrap test, this method of obtaining a confidence interval is best performed on a variance stabilized scale. The confidence interval is thus calculated on the variance

stabilized scale and back transformed to obtain an interval on the original scale. (*See details in Part D below*)

D) Variance stabilizing transformation

The bootstrap hypothesis test presented in Part B gives different results if a different scale is used for the bootstrap differences in means M_b^*, and will perform best on a variance stabilized scale where M and SE(M) are independent.

The test will be carried out after a variance stabilizing transformation of the bootstrap values M_b^*, say function ***g***. Note that this is not the same as transforming the data since transforming the bootstrap values M_b^* will still allow a comparison of arithmetic means.

The test statistic calculated for each resample is then given by

$$T_b^* = g(M_b^*) - g(M).$$

There is no longer a need to divide by the estimated standard error because on the variance stabilized scale this will be constant.

An estimate of the P-value for the test is then obtained by comparing the observed value of the test statistic

$$t_{obs} = g(M) - g(M_0),$$

(where M_0 is the null value for the difference in means, usually 0) with the distribution of T_b^* values.

If none of the values of M_b^* is equal to 0, then $g(M_0)$ is interpolated by

$$g(M_0) = \frac{g(M_{0-}) + g(M_{0+})}{2},$$

where M_{0+} is the smallest value of M_b^* that is greater than 0 and M_0- is the greatest value of M_b^* that is less than 0. In cases where M_{0+} does not exist, $g(M_0)$ is estimated by $g(M_{0-})$. In cases where M_{0-} does not exist, $g(M_0)$ is estimated by $g(M_{0+})$.

Details of an `automatic' method of finding an approximate variance stabilizing transformation ***g*** are given below. It was recommended to base this 'automatic' method on a Taylor series argument. For a random variable X with mean M and standard deviation s(M) that varies as a function of M, the transformation given by

(1)

$$g(x) = \int^{x} \frac{1}{s(u)}\,\mathrm{d}u$$

has the property that the variance of g(X) is approximately constant.

The Non-Parametric Bootstrap-t Method with a variance stabilizing transformation

The following steps describe the variance stabilized non-parametric bootstrap-t method for a difference in means:

1. Form a set of B bootstrap data sets sampled with replacement from the two groups Y and Z, as described in Part A). The number of replications B in this analysis is 10000.
2. Compute the difference in means Mb* and standard error SEb* for each bootstrap data set, b=1, 2,..., B.
3. Fit a curve to the points [M_b^* and SE_b^*] using a non-linear regression technique to produce a smooth function s such that $s(M_b^*)$ is the average SE_b^* at M_b^*, using quadratic polynomials (degree 2) for the local regression and cubic interpolation polynomials in the blending method of the local polynomial fits. The generalized cross-validation smoothing criterion (GCV) is applied for the fit.

   The size of the local neighborhood in the local fitting is determined by the value of the smoothing parameter (θ), which indicates the proportion of the data points used for the local fitting. The value of the smoothing parameter θ that is used is obtained by minimizing the generalized cross- validation smoothing criterion (GCV). The cubic interpolation method assumes that the maximum number of points in the leaf nodes of the kd tree (bucket size) is set to θ*k/5, where θ is the estimated smoothing parameter and k is the number of observations being used.
4. Estimate the variance stabilizing transformation g(M) using equation (1) and a numerical integration technique. For the present analysis, the Simpson's numerical integration method will be used.
5. Compute a bootstrap-t confidence interval for the transformed values $g(M_b^*)$ in the way described previously in Part C, where α=0.05. The standard error will be approximately constant, so SE_b^* and SE(g(M)) can be set equal to 1. Thus the CI for the transformed values will be calculated as follows:

   $$(g(M) - T^*_{(1-\alpha/2)}, \quad g(M) - T^*_{(\alpha/2)}),$$

   where $T^*_{(1-\alpha/2)}$ and $T^*_{(\alpha/2)}$ are the percentiles of $T_b^* = g(M_b^*) - g(M)$.

   Estimate the p-value for the hypothesis test as described previously in Part D.
6. The endpoints (ie, the estimated difference in means and the CI) calculated on the transformed scale can be mapped back to the original scale using the inverse transformation g^{-1}. Of note, when the value falls in between two existing values in the lookup table, the inverse transformation g^{-1} will be calculated using linear interpolation.

   (Programming note: For the CI, in the case where the CI exact limits cannot be determined because they fall outside the range of existing data, then the output will not display the limit which cannot be determined, but will display the following labels: "<min" or ">max", where applicable.)

   The adequacy of the transformation can be checked by plotting M_b^* against the standard error on the variance stabilized scale, an approximation of which is given using the delta method

$SE(g(M_b^*)) = SE_b^* / s(M_b^*)$

13.2 Handling of questionnaire data

The following rules will apply for analysis of (1) out of range and (2) ambiguous answers (ie, invalid or unable to interpret answers) to questionnaires completed by subjects:

In case of out of range answer (ie, an answer that does not correspond to any possible response proposed in the questionnaire, eg, "?", "I don't know," or any value superior or inferior to the ones specified in the response options): the answer will be scored "missing".

However, in case the subject selected one of the proposed responses but added a comment (for instance "6 +++" or "5 ?"), the response (ie, "6" or "5") will be retained for scoring but not the comment (ie, "+++" or "?").

In the same way, if the subject selected one of the proposed responses but added a value superior or inferior to the ones specified in the responses options (for instance, "4/5" or "-1/2" on a 5-point scale ranging from 0 to 4), the response corresponding to the possible responses options (ie, "4" or "2") will be retained for scoring but not the values superior or inferior to the responses options (ie, "5" or "-1").

In case of ambiguous answer (ie, multiple responses to a question allowing only a single response, a response marked between two allowed responses):

Multiple responses to a question allowing only a single response:

- If half or more responses are marked (ie, 4 responses marked on a seven point scale, 3 responses marked on a 5-point scale, 2 responses to a Yes/No item…): the answer will be scored "missing".
- If less than half responses are marked:
  - if the responses are NOT adjacent to each other: the answer will be scored "missing",
  - if the responses are adjacent to each other ("2/3" or "2/3/4", for instance), the more severe score will be retained.

If a response is marked between two allowed responses (for instance, the subject marked his/her response between 2 and 3 on a 4-point scale allowing only responses 1, 2, 3 and 4): the nearest more severe score will be retained.

If a response expected to be stable over time (eg, education) is varying over time no corrective action is foreseen and data will be utilized as reported.

If the EQ-5D VAS contains 2 answers, the most severe answer will be retained.

Please see Section 8.3.1.9 for special rules applicable to the WPS.

13.3 ASAS-NSAID equivalent score

Table 13–1: ASAS-NSAID equivalent score

NSAID	Consensus dose comparable to 150mg of diclofenac (in mg)
Dicloflenac	-
Naproxen	1000
Aceclofenac	200
Celecoxib	400
Etodolac	600

NSAID	Consensus dose comparable to 150mg of diclofenac (in mg)
Etoricoxib	90
Flurbiprofen	200
Ibuprofen	2400
Indometacin	150
Ketoprofen	200
Meloxicam	15
Nimesulide	200
Phenylbutazone	400
Piroxicam	20
Tenoxicam	20

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

STATISTICAL ANALYSIS PLAN

Study: AS0006 (C-AXSPAND)

Product: Certolizumab pegol

PHASE 3, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO EVALUATE EFFICACY AND SAFETY OF CERTOLIZUMAB PEGOL IN SUBJECTS WITH ACTIVE AXIAL SPONDYLOARTHRITIS (AXSPA) WITHOUT X-RAY EVIDENCE OF ANKYLOSING SPONDYLITIS (AS) AND OBJECTIVE SIGNS OF INFLAMMATION

SAP/Amendment Number	Date
Final SAP	14 Jan 2015
SAP Amendment 1	22 Apr 2016
SAP Amendment 2	08 June 2017
SAP Amendment 3	26 March 2018

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADAb	Anti-drug antibody
ADaM	analysis data model
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
ASAS	Assessment of SpondyloArthritis international Society
ASAS20, 40	Assessment of SpondyloArthritis international Society 20%, 40% response criteria
ASAS5/6	Assessment of SpondyloArthritis international Society 20% improvement in 5 of 6 domains
AS	ankylosing spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASDAS-CII	Ankylosing Spondylitis Disease Activity Score – Clinically Important Improvement
ASDAS-HD	Ankylosing Spondylitis Disease Activity Score – High Disease activity
ASDAS-ID	Ankylosing Spondylitis Disease Activity Score – Inactive Disease
ASDAS-MD	Ankylosing Spondylitis Disease Activity Score – Moderate Disease
ASDAS-MI	Ankylosing Spondylitis Disease Activity Score – Major Improvement
ASDAS-vHD	Ankylosing Spondylitis Disease Activity Score – very High Disease activity
ASQoL	Ankylosing Spondylitis Quality of Life
ASspiMRI-a	Ankylosing Spondylitis spine MRI scoring system for disease activity

AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AU	Anterior Uveitis
AxSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASDAI50	Bath Ankylosing Spondylitis Disease Activity Index 50% response criteria
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMI	body mass index
BMP	bone morphogenic protein
BP	bodily pain
CI	confidence interval
CK	creatinine kinase
CR	compliance ratio
CRP	C-reactive protein
CSR	clinical study report
CV	coefficient of variation
CZP	certolizumab pegol
DEM	Data Evaluation Meeting
DKK1	dickkopf-related protein 1
DRL	Drug Reference List
DMARD	disease-modifying antirheumatic drug
EAIR	exposure-adjusted incidence rate
EAER	exposure-adjusted event rate

eCRF	electronic case report form
EQ-5D	EuroQoL Health Status Questionnaire (5 dimensions)
ER	emergency room
ES	Enrolled Set
FAS	Full Analysis Set
GH	general health
HCQ	hydroxychloroquine
HLA-B27	human leukocyte antigen B27
HLT	High Level Term
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation
IXRS	interactive response system
IBD	inflammatory bowel disease
LOCF	last observation carried forward
LLN	lower limit of normal
LLOQ	lower limit of quantification
LLT	Low Level Term
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCS	Mental Component Summary
MedDRA®	Medical Dictionary of Regulatory Activities®
MH	mental health
MMP	matrix metalloproteinase
mNY	Modified New York (criteria)
MOS	Medical Outcomes Study

MRI	magnetic resonance imaging
MTX	methotrexate
nADA	neutralizing ADAb
NRS	Numeric Rating Scale
NRI	non-response imputation
NSAID	nonsteroidal anti-inflammatory drug
OC	observed case
OL	Open-label
OL-CZP	Open-label CZP
OL-OT	Open-label Other Treatment
PBO	placebo
PCS	Physical Component Summary
PF	physical Function
PGADA	Patient's Global Assessment of Disease Activity
PhGADA	Physician's Global Assessment of Disease Activity
PPS	Per Protocol Set
PT	Preferred Term
Q	question
Q1	1st Quartile
Q3	3rd Quartile
Q2W	every 2 weeks (every other week)
QoL	quality of life
RBC	red blood cell
RCTC	Rheumatology Common Toxicity Criteria

RE	role emotional
RP	role physical
RS	Randomized Set
SAARD	slow-acting anti-rheumatic drug
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SD	standard deviation
SDTM	study data tabulation model
SE	standard error
SF	social functioning
SFE	Safety Follow-up Extension
SF-36	Short-Form 36-Item Health Survey
SI	sacroiliac
SJC	swollen joint count
SLPQRAW	Sleep Quantity Raw Score
SLPOP1	Optimal Sleep
SM	spinal mobility
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	standard operating procedure
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
sqrt	square root
SS	Safety Set

SSZ	sulfasalazine
STIR	short-tau-inversion recovery
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF	tumor necrosis factor
USA	United States of America
ULN	upper limit of normal
VAS	visual analog scale
VT	vitality
VU	vertebral units
WBC	white blood cell
WHO	World Health Organization
WPS	Work Productivity Survey

1 INTRODUCTION

This SAP describes the analysis of the double-blind 52-week treatment period and the 10-week follow-up period of the C-axSpAnd (AS0006) study. It is designed to support a Clinical Study Report (CSR), is compliant with International Conference on Harmonization (ICH) guidelines and is based on the Protocol Amendment 3 dated 13 February 2017.

2 PROTOCOL SUMMARY

The C-axSpAnd study (AS0006) is a randomized, double-blind, parallel-group, placebo-controlled study, consisting of 52 weeks of treatment with certolizumab pegol (CZP), followed by a follow-up period for 8 weeks after the Week 52/Withdrawal [WD] visit which is 10 weeks after the last administration of study medication, or at the completion of the Week 52 visit assessments, eligible subjects may receive open-label CZP treatment for an additional 2 years in an open-label Safety Follow Up Extension (SFE) Period.

The study population is subjects with active axial spondyloarthritis (axSpA) with sacroiliitis on magnetic resonance imaging (MRI) or C-reactive protein (CRP) levels indicative of inflammatory disease but without x-ray evidence of ankylosing spondylitis (AS) who have had an inadequate response to, have a contraindication to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Eligible subjects will be allocated to the following study treatments in a 1:1 ratio:

- CZP administered subcutaneously (sc) at the dose of CZP 400mg at Weeks 0, 2, and 4 followed by CZP 200mg every other week (Q2W) starting at Week 6
- Placebo

2.1 Study objectives

2.1.1 Primary objective

The primary objective of the study is to demonstrate the efficacy of CZP 200mg Q2W on the signs and symptoms of subjects with active axSpA without x-ray evidence of ankylosing spondylitis.

2.1.2 Secondary objectives

The secondary objectives of the study are to assess efficacy, safety, and tolerability and to demonstrate the effect of CZP on:

- Health outcomes
- Disease activity
- SI joint inflammation
- Changes to concomitant and background medications

2.1.3 Other objectives

The other objectives of the study are to assess the effects of CZP on the following:

- Spinal mobility
- Total and nocturnal spinal pain numeric rating scale (NRS)

- Spinal inflammation
- SI joint structural changes
- Treatment response over time
- Signs and symptoms of the disease
  - Morning stiffness
  - Fatigue
  - Extra articular manifestations of axSpA
  - Sleep
  - Physical function
- Subject's health status
- Acute phase reactant (CRP)
- Health-related quality of life
- Work and household productivity
- Pharmacokinetics and immunogenicity

2.1.4 Pharmacogenomics objectives

The pharmacogenomics objectives are to assess the effect of CZP on gene and protein expression and to explore the relationship between genomic biomarkers and disease biology, drug treatment and inflammatory and immune responses (for those subjects who consent to the genomics sub-study)

2.2 Study variables

2.2.1 Efficacy variables

2.2.1.1 Primary efficacy variable

- ASDAS-MI response at Week 52

For Canada (and any other country where applicable or where requested by Regulatory Authorities), the primary efficacy variable is:

- Assessment of SpondyloArthritis international Society 40% response criteria (ASAS40) response at Week 12

2.2.1.2 Secondary efficacy variables

- ASAS40 response at Weeks 12 and 52
- Change from Baseline in BASFI at Weeks 12 and 52
- Change from Baseline in BASDAI at Weeks 12 and 52
- Change from Baseline in Sacroiliac (SI) joint SPARCC score at Week 12
- Number of subjects without relevant changes to background medication

- Change from Baseline in ASQoL at Week 52
- Change from Baseline in ASQoL at time points other than Week 52
- Change from Baseline in nocturnal spinal pain (NRS) at Week 52
- Number of subjects with Anterior Uveitis (AU) or new AU flares through Week 52

For Canada (and any other country where applicable or where requested by Regulatory Authorities), the secondary efficacy variables are:

- ASAS40 response at Week 52
- ASDAS-MI at Week 52
- Change from Baseline in BASFI at Weeks 12 and 52
- Change from Baseline in BASDAI at Weeks 12 and 52
- Change from Baseline in SI joint SPARCC score at Week 12
- Number of subjects without relevant changes to background medication
- Change from Baseline in ASQoL at Week 52
- Change from Baseline in ASQoL at time points other than Week 52
- Change from Baseline in nocturnal spinal pain (NRS) at Week 52
- Number of subjects with AU or new AU flares through Week 52

2.2.1.3 Other efficacy variables

The following variables will be analyzed at scheduled time points through Week 52:

- ASAS 20% response criteria (ASAS20), ASAS40, ASAS 20% improvement in 5 of 6 domains (ASAS5/6), and ASAS partial remission response
- Change from Baseline in individual ASAS components:
  - Patient's Global Assessment of Disease Activity (PGADA)
  - Total and nocturnal spinal pain (NRS)
  - BASFI
  - Average of questions 5 and 6 of the BASDAI concerning morning stiffness
  - BASMI lateral spine flexion
  - CRP
- Change from Baseline in BASDAI and individual questions 1, 2, 3 and 4
- Change from Baseline in ASDAS
- Change from BASMI linear
- ASDAS disease activity (ASDAS-ID, ASDAS-MD, ASDAS-HD, ASDAS-vHD) and clinical improvement (ASDAS-CII, ASDAS-MI)

- BASDAI50 response
- Change from Baseline in Fatigue (NRS) (from BASDAI)
- Change from Baseline in SI grading to Week 52 for structural damage
- Change from Baseline in SI joint SPARCC score at Week 52 and ASspiMRI-a in the Berlin modification at Week 12 and Week 52
- Proportion of subjects with SI joint SPARCC score <2 at Week 12 and Week 52
- Change from Baseline in ASQoL
- Change from Baseline in ASAS-NSAID score
- Number of AU flares
- Number of inflammatory bowel disease (IBD) exacerbations
- Number of psoriasis exacerbations
- Work Productivity Survey (WPS)
- Change from Baseline in the Sleep Problems Index II domains of the MOS Sleep scale
- Change from Baseline in enthesitis Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)
- Change from Baseline in swollen and tender joint counts (44 joint count)
- Change from Baseline in Physician's Global Assessment of Disease Activity (PhGADA)
- Change from Baseline in the SF-36 PCS and MCS
- Change from Baseline in the SF-36 domains:
  - Role Physical
  - Bodily Pain
  - General Health
  - Vitality
  - Social Functioning
  - Role Emotional
  - Mental Health
- Health status as assessed by the EuroQoL Health Status Questionnaire (5 dimensions) (EQ-5D) domains, visual analog scale (VAS) actual score, and change from Baseline in VAS score
- Resources utilization: concomitant medical procedures, health care provider consultations not foreseen by the protocol, hospitalizations/emergency room visits

2.2.2 Pharmacokinetic/pharmacogenomics variables and biomarkers

2.2.2.1 Pharmacokinetic variables

Certolizumab pegol plasma concentrations will be measured and summarized at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52, and at the Follow-up visit (8 weeks after the Week 52/WD Visit).

These plasma samples may be used additionally for analyses of CZP and/or its constituent moieties, using alternative methods.

2.2.2.2 Biomarkers and cytokines

Selected samples collected for measurement of CZP plasma concentration may be used additionally for analyses of candidate biomarkers and cytokines, where appropriate. The biomarkers to be analyzed may include, but will not be limited to, the following:

Matrix metalloproteinase-3 (MMP-3), Bone morphogenic protein BMP-2,-4 and -7, wingless related mouse mammary tumor virus integration site protein (WNT1) - Inducible Signaling Pathway proteins (WISP), Gremlin, Dickkopf-related protein 1 (DKK1), Sclerostin, Hedgehog proteins (Shh, Ihh, Dhh), Collagen turnover/cleavage products, collagen type X, Vascular Endothelial Growth Factor (VEGF), citrullinated vimentin fragments, cytokines: IL13, IL17 A and F, IL23, IL34, Transforming Growth Factor (TGF) β, Macrophage colony-stimulating factors (M-CSF), Granulocyte macrophage colony-stimulating factor (GM-CS), colony-stimulating factor -1 (CSF-1), soluble CSF-1 Receptor (sCSF1r) levels.

2.2.2.3 Pharmacogenomics variables

For individuals consenting to the genomics substudy, blood samples will be drawn for possible genetic/epigenetic, genomic, proteomic, and metabolomics analysis at Baseline and Week 12. Additional samples will be collected for genomics, proteomics, and metabolomics analysis only, at Baseline, Weeks 4, 12, and 52/WD. Collection of the samples will enable exploratory evaluation of biomarkers relative to disease biology, drug treatment and inflammatory and immune response processes. The nature and format of these tentative analyses will be determined when the results of the main study are made available. The samples will be stored at -80°C at the central biorepository for up to 20 years.

2.2.3 Immunological variables

Anti-drug antibody (ADAb) (Anti-CZP antibody) concentrations will be assessed at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52/WD, and the FU visit (8 weeks after the Week 52/WD visit). In addition, the ADAb will be assessed in subjects who withdraw from double-blind study drug and transition to open-label CZP prior to Week 52.

Determination of ADAb will be done using a validated screening, confirmation and titration ADAb bridging assay, with potential further characterization by a neutralizing antibody assay. The immunogenicity data will be processed according to dedicated Bioanalytical Analysis plans.

The following variables will be analyzed as described in Section 10:

- Anti-CZP antibodies at Baseline, Weeks 1, 2, 3, 12, 24, 36 and 52/WD
- Status of ADAb (including overall, baseline and treatment-emergent classification)
- ADAb response characterized for their neutralizing potential

2.2.4 Safety variable(s)

2.2.4.1 Adverse events

Presence (Y/N) of

- Adverse Event (AE)
- Serious AE
- Non-serious AE
- Death
- AE leading to permanent withdrawal of study medication
- Severe AE
- Drug-related AE
- AE of special interest
  - Serious infections including opportunistic infections
  - Malignancies including lymphoma
  - Serious cardiovascular events
  - Congestive heart failure
  - Demyelinating-like disorders
  - Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia and leucopenia
  - Serious bleeding events
  - Lupus and lupus-like illness
  - Serious skin reactions (eg, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

2.2.4.2 Laboratory parameters

- Change from Baseline in hematology parameters at Weeks 2, 4, 8, 12, 24, 36, 52/WD and the Follow-up visit
  - Red blood cells
  - Hemoglobin
  - Hematocrit
  - Platelets
  - White blood cells
  - Neutrophils
  - Lymphocytes
  - Monocytes

  - Eosinophils
  - Basophils
- Change from Baseline in hematology parameters to minimum post-Baseline value, maximum post-Baseline value, and last value
  - Red blood cells
  - Hemoglobin
  - Hematocrit
  - Platelets
  - White blood cells
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
- Change from Baseline in serum biochemistry parameters Weeks 2, 4, 8, 12, 24, 36, 52/WD, and the Follow-up visit
  - Sodium
  - Potassium
  - Chloride
  - Bicarbonate
  - Total calcium
  - Inorganic phosphorus
  - CRP (already included in efficacy section)
  - Creatinine kinase (CK)
  - Glucose
  - Creatinine
  - Uric acid
  - Urea
  - Total protein
  - Albumin
  - Alkaline phosphatase (AP)
  - Aspartate aminotransferase (AST)

  - Alanine aminotransferase (ALT)
  - Bilirubin
  - Total cholesterol
- Change from Baseline in serum biochemistry parameters to minimum post-Baseline value, maximum post-Baseline value, and last value
  - Sodium
  - Potassium
  - Chloride
  - Bicarbonate
  - Total calcium
  - Inorganic phosphorus
  - CRP (already included in efficacy section)
  - Creatinine kinase (CK)
  - Glucose
  - Creatinine
  - Uric acid
  - Urea
  - Total protein
  - Albumin
  - Alkaline phosphatase (AP)
  - Aspartate aminotransferase (AST)
  - Alanine aminotransferase (ALT)
  - Bilirubin
  - Total cholesterol
- Urinalysis status at Weeks 2, 4, 8, 12, 24, 36, 52/WD, and the Follow-up visit
  - PH
  - Protein
  - Glucose
  - Blood
  - Esterase
- Hematology parameter normal range classification at Weeks 2, 4, 8, 12, 24, 36, 52/WD, and the Follow-up visit

  - Red blood cells
  - Hemoglobin
  - Hematocrit
  - Platelets
  - White blood cells
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
- Serum biochemistry parameter normal range classification at Weeks 2, 4, 8, 12, 24, 36, 52/WD, and the Follow-up visit
  - Sodium
  - Potassium
  - Chloride
  - Bicarbonate
  - Total calcium
  - Inorganic phosphorus
  - CRP (already included in efficacy section)
  - Creatinine kinase
  - Glucose
  - Creatinine
  - Uric acid
  - Urea
  - Total protein
  - Albumin
  - Alkaline phosphatase
  - Gamma glutamyl transferase
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Bilirubin

  - Total cholesterol

- Hematology parameter marked abnormality classification (Rheumatology Common Toxicity Criteria [RCTC]) Weeks 2, 4, 8, 12, 24, 36, 52/WD, and the Follow-up visit
  - Hemoglobin
  - Platelets
  - White blood cells
  - Neutrophils
  - Lymphocytes
- Serum biochemistry parameter marked abnormality classification (RCTC) Weeks 2, 4, 8, 12, 24, 36, 52/WD, and the Follow-up visit
  - Sodium
  - Potassium
  - Total calcium
  - Creatinine kinase
  - Glucose
  - Creatinine
  - Uric acid
  - Alkaline phosphatase
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Bilirubin
- Presence (Y/N) of liver parameter elevations above upper limit of normal (ULN)
  - 3x ULN elevations of AST
  - 5x ULN elevations of AST
  - 10x ULN elevations of AST
  - 20x ULN elevations of AST
  - 3x ULN elevations of ALT
  - 5x ULN elevations of ALT
  - 10x ULN elevations of ALT
  - 20x ULN elevations of ALT
  - 3x ULN elevations of either AST or ALT
  - 5x ULN elevations of either AST or ALT

- 10x ULN elevations of either AST or ALT
- 20x ULN elevations of either AST or ALT
- 1x ULN elevations of bilirubin
- 1.5x ULN elevations of bilirubin
- 1.5x ULN elevations of AP
- 1x ULN elevation of bilirubin and 3x ULN elevation of either ALT or AST

2.2.4.3 Vital signs

- Change from Baseline in vital signs at Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44 , 46, 48, 50, 52/WD, and the Follow-up visit
  - Pulse rate
  - Systolic blood pressure
  - Diastolic blood pressure
  - Temperature
  - Respiration rate
- Change from Baseline in vital signs to minimum post-Baseline value, maximum post-Baseline value, and last value
  - Pulse rate
  - Systolic blood pressure
  - Diastolic blood pressure
  - Temperature
  - Respiration rate

2.2.4.4 Other safety variables

- Change from Baseline in weight at Weeks 12, 16, 24 and 52/WD
- Signs and symptom of latent or active TB completed at Baseline, Weeks 12, 24, 36 and 52/WD
- TB risk factors
- Occurrence of pregnancy through to Week 52/WD and Follow-up visit

2.3 Study design and conduct

The C-axSpAnd study (AS0006) is a 52-week multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study to evaluate the efficacy and safety of CZP in adult subjects with active axSpA with sacroiliitis on magnetic resonance imaging (MRI) and/or CRP levels indicative of inflammatory disease but without x-ray evidence of ankylosing spondylitis (AS) who have had an inadequate response to, have a contraindication to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs). At the completion of the Week 52

visit assessments, eligible subjects may receive open-label CZP treatment for an additional 2 years in an open-label, Safety Follow-up Extension (SFE) period.

2.3.1 Study periods

Period 1 (Screening period) – Screening period of 1 day to 6 weeks before Baseline in order to obtain laboratory data, to verify that the doses of methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), NSAIDs, and corticosteroids, if used, are stable, and to enable washout of any medications not permitted for use during the study, and initiation of latent TB treatment where necessary. Concomitant medications permitted during the study should remain stable for at least 4 weeks prior to Baseline at Week 0.

SI-joint x-rays (read centrally) will allow discrimination of subjects with (AS) and without definitive evidence for sacroiliitis on x-ray (modified New York [mNY]-negative-axSpA).

Enrolled subjects must undergo an MRI later during the Screening period for central reading with results from the central reading available by no later than at the Baseline visit.

Period 2 (Double-blind period) – Week 0 to Week 52, placebo-controlled.

Eligible subjects will be allocated to the following double-blind study treatments in a 1:1 ratio:

- CZP administered sc at the loading dose of CZP 400mg Q2W at Weeks 0, 2 and 4 followed by CZP 200mg Q2W (starting at Week 6)
- Placebo

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments (including placebo) will be administered sc at the study site. At the Week 0, 2, 4, 6, and 8 visits, the administration must be done by dedicated, unblinded, and adequately trained site personnel. At the Week 10 and 12 visits, the subject will receive training on self-injection and the study treatment will be self-administered under the supervision of the unblinded study personnel. At Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50, the study treatment administration should preferably be done by the unblinded study personnel, or alternatively by self-injection of the subject under the supervision of the unblinded study personnel.

Subjects who discontinue the double-blind study treatment and enter open-label treatment with CZP will be assessed 2 and 4 weeks after open-label CZP treatment has been initiated and every 12 weeks thereafter. Alternatively, subjects who discontinue the double-blind study treatment and receive other treatment (including biologics) will be assessed every 12 weeks after initiation of the open-label other treatment (OL-OT). In either alternative schedule, assessments should be conducted until as close as possible to Week 52 (within ± 4 weeks), where Week 52 is relative to the original randomization at Week 0. Subjects will then be invited to the Week 52 assessment visit.

Period 3 (Follow-up period) - All subjects not participating in the SFE period after Week 52, including those withdrawn from the study prematurely, will have a single Follow-up visit, 8 weeks after Week 52/WD visit (10 weeks after their last administration of study medication).

SFE Period - Week 52 to Week 156, open-label:

At the completion of the Week 52 visit assessment, subjects on double-blind study treatment may receive open-label CZP treatment for an additional 2 years. Subjects who withdrew from double-blind study treatment and transitioned to open-labelCZP treatment are also eligible to participate in the SFE period after completing the Week 52 visit assessment. Subjects on OL-OT are not eligible to participate in the SFE period.

Eligible subjects are allowed to roll-over to the SFE-period up to 3 months after completion of the Week 52 assessments.

Starting at Week 64, all subjects are to visit the site approximately every 12 weeks for assessments. The last dosing visits will be at Week 154. The final study assessments are performed at Week 156.

The schedule of study assessments is provided in Section 5.2 of the protocol.

A schematic diagram of the study design is provided in Section 5.3 of the protocol.

2.3.2 Study duration per subject

For each subject, the first 3 periods of the study will last a maximum of 66 weeks, as follows:

- Up to 6 weeks in the Screening period
- 52 weeks in the double-blind period
- A Follow-up visit, 8 weeks after Week 52/WD visit for subjects not participating in the SFE Period.

For subjects participating in the SFE period, the study will extend up to a maximum of 104 additional weeks.

The end of the study will be defined as the date of the last subject's last visit, defined as the Follow-up Visit 8 weeks after Week 52/WD visit for subjects not participating in the SFE Period, or the last visits of the SFE Period.

2.3.3 End of periods and study

The end of the study is defined as the date of the last visit (including Follow-up visit and SFE period) of the last subject in the study. Period start and ends are defined in Section 3.2.1.

2.3.4 Planned number of subjects and sites

Approximately 1200 subjects are expected to enter the Screening period in order to have 300 subjects randomized into the double-blind period. It is planned to enroll the subjects at approximately 120 sites.

2.3.5 Anticipated regions and countries

The study will be conducted in North America, Australia, Europe, Asia, and other regions as appropriate.

2.3.6 Stratification

Randomization will be stratified on:

- Region
  - North America: Canada and USA

  - Europe: Bulgaria, Czech Republic, Hungary, Poland and Russia
  - Asia: Australia, Hong Kong, Taiwan and Singapore

- MRI/CRP classification

Subjects will be classified as MRI+/- depending on whether or not they have evidence of sacroiliitis on MRI at Screening based on the ASAS/OMERACT definition. Subjects will be classified as CRP+/- based on the CRP value obtained at the second Screening visit scheduled to occur 3 to 5 days prior to Baseline. Subjects will be categorized as CRP+ if their CRP value is above the level indicative of inflammatory disease at this visit. Otherwise, they will be considered CRP-. Based on these definitions, the stratification for MRI/CRP classification will have the following 3 levels:

- MRI+/CRP+
- MRI+/CRP-
- MRI-/CRP+

Subjects who are MRI-/CRP- are not eligible for randomization. The interactive response system (IXRS) will be designed to ensure that at least 20% of the randomized subjects belong to one of the three clinical subgroups above.

2.4 Determination of sample size

Subjects will be randomized in a 1:1 ratio to the CZP 200mg Q2W and placebo treatment groups. The expected response rates for ASDAS-MI at Week 52 are 40% and 20% for CZP and placebo, respectively. A total sample size of 300 (150 subjects per treatment group) provides 95% power to detect a statistically significant difference in the ASDAS-MI response rate at Week 52 between CZP and placebo based on a 2-sided significance level of 0.05.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

All statistical analyses will be performed using SAS® (STATISTICAL ANALYSIS SYSTEM, SAS-Institute, Cary, NC, USA) according to UCB SOPs.

For continuous data in general, summary statistics (n [number of available measurements], arithmetic mean, SD, median, minimum, and maximum) will be presented by treatment group. For selected variables, the first (25^{th} percent) quartile (Q1) and the third (75^{th} percent) quartile (Q3) may also be presented (for patient reported outcomes).

Mean, SD, median and quartiles will be displayed to 1 more decimal place than collected in the source data. Derived variables in general will display the mean, SD and median to 1 more decimal place than the variables used in the derivation (i.e. a change from Baseline will be reported to the same precision as the Baseline data). However, a special rule can be defined as needed for appropriate reporting.

For descriptive statistics of continuous variables by visit, the change from Baseline and actual value at the given time point will be displayed. The change from Baseline is the post-Baseline value minus the Baseline value. If the Baseline or post-Baseline value is missing, then the change from Baseline is set to missing. Percent change from Baseline is the change from

Baseline divided by Baseline and multiplied by 100. If the Baseline value is 0 and the post-Baseline value is also 0, then the percent change from Baseline is set to 0. If the Baseline value is 0 and the post-Baseline value is non-zero, then the percent change from Baseline is set to missing. If the Baseline value is missing, the percent change from Baseline is set to missing.

Frequency tables (frequency counts and percentages) will be presented for categorical data. If there are no missing values then the missing row can be removed. If there are missing values (including missing a single assessment or entire visit), then include the missing row with the frequency count and percentage. If there are no subjects in a specific electronic case report form (eCRF) category, then that row will be retained and 0 presented in the table.

In general, percentages will be calculated based on the utilized analysis set. However, in the case of subgroup analyses, the N of the subgroup will be used as denominator.

Unless stated otherwise, all inferential statistical tests will be 2-sided and conducted at the 0.05 alpha level. P-values will be presented to 3 decimal places. Relevant SAS output will be included in the 'Documentation of Statistical Methods' section of the CSR. All data in the database (SDTM and ADaM) will be presented in by-subject data listings, and sorted by treatment group, site, subject number, and visit (where applicable).

A fixed-sequence testing procedure will be used to control the overall Type 1 error for comparison of multiple efficacy endpoints. This procedure is described in Section 8.

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 Pre-treatment period

The pre-treatment period (Screening period) of the study is the period prior to a subject's first dose of study medication administration. This period starts at the Screening visit (week -6 to -1 day) and ends at the Baseline visit (Week 0) up to the time of first study medication administration (exclusive). Unless specific time information is available to indicate that a Screening or Baseline visit assessment was performed after a subject's first study medication administration, all assessments will be attributed to the Screening period.

3.2.1.2 Double-blind treatment period

The double-blind treatment period begins at the Baseline visit (Week 0) at the time of first study medication administration (inclusive) and ends when:

- the subject takes their first dose of open-label CZP (OL-CZP) or open-label other treatment (OL-OT) for those who continue into the SFE or who switch to OL-CZP or OL-OT
- the later of Week 52 visit and last administration of double-blind treatment, for subjects who complete the 52 week main phase of the study and do not continue into the SFE and who do not switch to OL-CZP or OL-OT
- the subject discontinues the study on double-blind treatment prior to the week 52 visit (WD visit) and does not fall into the above categories.

For subjects who prematurely withdraw from the study prior to Week 52 (for example, those who cease to have double-blind and open-label visit data collected), their visit assessments at withdrawal will be assigned to the next scheduled visit following the last visit where assessments

are available according to each protocol activity. This could be the next double-blind or open-label visit. All visit measurements, even violating the visit window, will be utilized for the respective visit as long as they are in the proper sequence.

Subjects will be classified as completing the main phase of the study if they complete the Week 52 visit without early withdrawal during the main phase of the study. This is regardless of whether they attend the Follow-up visit or enter SFE period and regardless of whether they are on double-blind treatment, OL-CZP, or OL-OT.

3.2.1.3 Open-label period

The open-label period starts when subjects have discontinued the double-blind treatment period prior to start of the SFE period and take their first dose of open-label CZP or other treatment. The open-label period ends when:

- the subject takes their first dose of OL-CZP in the SFE period, for subjects continuing into the SFE
- the later of Week 52 visit and last administration of OL-CZP or other treatment, for subjects who complete the 52 week main phase of the study and do not continue into the SFE
- the subject discontinues the study prior to the week 52 visit (WD visit) and does not fall into the above categories.

Subjects switching from double-blind treatment to OL-CZP treatment and then to OL-OT will have an OL-CZP and an OL-OT period.

Subjects continuing on the study with other treatment visits, but without taking other medication will be allocated to the OL-OT period although will not be considered as starting other treatment in that period. A medical review of all cases will be performed prior to the database lock to identify subjects with valid administration of other treatment. Start and end dates of identified other treatments will be taken from the concomitant medication page.

The use of open-label period data for efficacy is described in detail in the relevant efficacy sections in Section 8. If applicable, open-label period data for efficacy will be mapped to the corresponding time-point post baseline for analysis. E.g. if a subject performs an open-label Week 12 visit at 26 weeks post-baseline, corresponding efficacy data will be considered "week 26" assessments.

Open-label visit-based safety data (such as laboratory data and vital signs data) will in general be summarized and listed as separate visits from the double-blind period visits. However, open-label visits will still be presented by the double-blind treatment groups of CZP 200mg Q2W and placebo. In general, OL-OT safety data will not be presented in tables, but only listed.

For subjects who receive OL-CZP, data will be presented by the OL-CZP visits. Safety summaries which are summarized 'At any visit', 'post-Baseline' (including minimum or maximum post-Baseline) or 'On treatment' will be presented separately for each period (double-blind and OL-CZP).Visit based efficacy or safety data that is recorded on the day of first administration of OL-CZP or OL-OT will be assigned to the previous period unless available time information clearly indicates that it was recorded after the first administration of OL-CZP or OL-OT.

Concomitant medications will be assigned to all periods (double-blind, OL-CZP, OL-OT or SFE) according to the rules given in Section 6.4.

AEs will be assigned to a period based on whether the AE started during the double-blind, OL-CZP, OL-OT period or SFE period. See Section 11.2 for more detail.

All data reported will be listed.

3.2.1.4 Follow-up period

For subjects not entering the SFE period (no SFE informed consent), the Follow-up period will start after the later of Week 52 visit or last study medication administration (for subjects having Week 52 visit on double-blind or open-label therapy) or after the WD visit. Visit based efficacy or safety data that is recorded at the Week 52 or WD visit will be assigned to the previous period.

The Follow-up period will end on the Follow-up visit date. The Follow-up visit will take place 10 weeks after the last dose of study medication, which should be 8 weeks after the Week 52 visit (if the Week 52 is the last non-Follow-up visit) or less than 10 weeks after the WD visit (if the WD visit is the last non-Follow-up visit).

3.2.1.5 SFE period

The SFE period starts when the subject takes their first dose of OL-CZP that is after week 50 and after date of informed consent for the SFE. Visit based efficacy or safety data that is recorded on the day of the first SFE period dose will be assigned to the previous period unless available time information clearly indicates that it was recorded after the first administration of SFE period treatment.

The SFE period ends when the subject discontinues from or completes the study following SFE enrollment.

3.2.2 Relative day

The relative day will be included in the listings and will be calculated as follows:

- If the start (stop) date occurred on or after the first dose, and on or prior to the double-blind drug stop date, relative day is calculated as start (stop) date minus first double-blind dose date + 1. Relative day will be prefixed by a ‘d’ in the listings to show it’s relative to double-blind treatment.
- For subjects not entering the OL-CZP period (including SFE period), if the start (stop) date occurred after the last dose of double-blind drug, the relative day to the most recent double-blind dose is calculated as start (stop) date minus most recent double-blind dose date. The relative day in this situation should be preceded by a ‘d+’.
- For subjects entering the OL-CZP period (including SFE period), if the start (stop) date occurred on or after the first OL-CZP start date, and on or prior to the OL-CZP stop date (including SFE period), relative day is calculated as start (stop) date minus first open-label dose date + 1. The relative day in this situation should be preceded by a ‘o’.
- For subjects entering the OL-CZP period (including SFE period), if the start (stop) date occurred after the last dose of OL-CZP drug, the relative day to the most recent OL- CZP dose is calculated as start (stop) date minus most recent OL-CZP dose date. The relative day in this situation should be preceded by a ‘o+’

- If the start (stop) date occurred before the first dose, the relative day is calculated as start (stop) date minus first dose date. The relative day in this situation should be preceded by a 'd-'.

Relative day will only be computed for fully completed dates and will be missing for partial dates. For AEs, relative days for start and stop dates will be calculated as the number of days since the first injection of the relevant double-blind or OL-CZP medication. For non-treatment emergent AEs, relative day of onset will be negative if the event started and stopped before the first dose.

3.3 Definition of Baseline values

Unless otherwise specified, the last valid measurement before study medication administration in the double-blind period will be used as the Baseline value. The same Baseline definition will be used for the open-label period. For almost all variables, this will be the assessment made at the Baseline visit. However, for some variables (eg, demography) assessments are scheduled for the Screening visit only and not for the Baseline visit. In this case, the Screening value will be utilized as Baseline value. If a Baseline visit measurement is missing, and a Screening visit measurement is available, the Screening value will be utilized as Baseline. If a scheduled Baseline assessment is taken on the same day as first administration of study medication and no time is collected, it will be assumed to have been taken prior to study medication.

Baseline images, either spinal x-ray or MRI assessments, are required to evaluate study eligibility. Therefore, all Baseline images will be available prior to randomization into the study. SI joint x-rays should not be older than 12 months prior to Baseline and should be verified by central reading during the Screening period.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on study conduct or on the primary efficacy outcome for an individual subject. The criteria for identifying important protocol deviations will be defined within the specification of Protocol Deviations document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented prior to unblinding to confirm exclusion from analysis sets.

3.5 Analysis sets

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have given informed consent.

3.5.2 Randomized Set

The Randomized Set (RS) will consist of all subjects randomized into the study.

3.5.3 Safety Set

The Safety Set (SS) will consist of all subjects in the RS who have received at least one dose of study medication.

3.5.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the RS who have received at least 1 dose of study medication.

3.5.5 Per Protocol Set

The Per Protocol Set (PPS) will consist of subjects in the FAS without any important protocol deviations that may influence the validity of the primary efficacy data. Treatment compliance as defined in Section 7 may also be utilized. Important protocol deviations will be predefined and evaluated at the DEM prior to study unblinding at the Week 52 interim database lock. Protocol deviations occurring after Week 52 (for example, for subjects continuing in the SFE period) will not be considered for PPS impact as they occurred after assessment of the primary variable was performed.

3.5.6 SFE Safety Set

The SFE Safety Set (SFE-SS) will be defined as all subjects who continued into the SFE Period and who received at least 1 dose of CZP in the SFE Period. Safety data recorded during the SFE will be presented alongside the Week 52 analyses and hence it is not expected that this analysis set will be required.

3.6 Treatment assignment and treatment groups

At Baseline, eligible subjects will be randomly assigned in a 1:1 ratio to the following double-blind study treatments:

- Placebo (PBO)
- CZP administered sc at the loading dose of CZP 400mg Q2W at Weeks 0, 2 and 4 followed by CZP 200mg Q2W (starting at Week 6)

For presentation purposes, the terms CZP 200mg Q2W and PBO will be used.

For disposition, demography, Baseline characteristics and protocol deviations, in addition to the CZP 200mg Q2W and PBO groups, an all subjects group (CZP 200mg and PBO combined) will be displayed.

In general, for by visit data collected during the open-label period, subjects will be presented according to the treatments received in the double-blind period (CZP 200mg Q2W and PBO). For the by visit data collected during the SFE period, subjects will be presented in a single CZP 200mg Q2W treatment group.

Concomitant medications will be summarized according to whether they were taken: during the double-blind period by CZP 200mg Q2W or PBO, or during the open-label period by PBO->OL CZP (subjects who were randomized to PBO and then received open-label CZP), CZP->OL CZP (subjects who were randomized to CZP and then received open-label CZP)- or by the OL-OT group. In addition, concomitant medications taken during any CZP medication period of the main study (Total CZP incl DB and OL) and all concomitant medications (All subjects, including OL-OT but excluding SFE) will also be summarized. See Section 6.4 for more detail.

AEs will be assigned to periods based on whether they started during the double-blind, OL-CZP, OL-OT, or SFE periods. Data corresponding to the OL-OT group will not be summarized, but only presented in listings. AEs will be summarized as follows:

- Double-blind period by CZP 200mg Q2W or PBO,
- Open-label CZP period by PBO->OL CZP or CZP->OL CZP (as above),
- SFE period by OL CZP
- Total CZP incl DB and OL (includes randomized CZP 200mg Q2W and AEs starting in the open-label CZP period).
- Total CZP incl DB, OL, and SFE OL (includes randomized CZP 200mg Q2W, AEs starting in the open-label CZP period and AEs starting in the SFE period).

See Section 11.2 for more detail.

If it is determined after unblinding that the subject received a treatment other than the one to which they were randomized, safety tables will still be based on the randomized treatment for the SS. However, additional safety tables based on the actual treatment received may also be prepared whereby all data taken on or after the 1st administration of CZP is summarized according to the CZP treatment group no matter which treatment they were randomized to. The efficacy analyses will strictly follow the intention to treat principle, and no correction for receiving incorrect treatment will be performed.

3.7 Center pooling strategy

Due to the anticipated low number of subjects per center, region is used as a randomization stratification factor. The regions utilized in the IXRS system (as described in Section 2.3.6) will be used to pool centers for statistical analysis. Verification that sufficient subjects within each region exist for meaningful statistical analysis will be performed prior to unblinding.

3.8 Coding dictionaries

Medical history and AEs will be coded using the latest version available for use at the time of study lock of Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Reference List (WHO-DRL).

3.9 Changes to protocol-defined analyses

The protocol stated that ADAb concentrations above 2.4 unit/ml would be defined as ADAb positive. However, during the trial it was noted that the background sample noise could only be determined during the sample analyses and hence the cut point cannot be pre-specified. Therefore the immunogenicity sections of the SAP were updated.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

Statistical models may be adjusted for covariates. Any such adjustments will be described in the context of the analyses to be performed.

4.2 Handling of dropouts or missing data

4.2.1 Primary efficacy variable

For analysis purposes, the primary efficacy variable is defined as a composite endpoint in which it is necessary to achieve ASDAS-MI at Week 52 and to remain on randomized double-blind study treatment through Week 52 in order to be considered a responder (Section 8.1). Subjects with missing ASDAS-MI at Week 52 are considered non-responders and therefore this composite endpoint definition does not allow for a missing response status and no formal method for handling missing data is needed in the primary efficacy analysis. However, in order to assess the impact of various missing data assumptions on the analysis, additional sensitivity analyses of the primary efficacy variable will be performed as follows:

- Including observed data at Week 52: The observed data at Week 52 will be used and analyzed according to randomized treatment, regardless of whether or not the subject is still on his/her randomized double-blind study treatment at that time. Therefore this is no longer a composite endpoint and subjects will be a responder based solely on if they achieve ASDAS-MI response. Despite efforts to continue to collect data on all subjects (even if they discontinue the double-blind study treatment), there may still be subjects with missing data at Week 52. Such subjects will be considered as non-responders. The same logistic regression model specified for the primary analysis will be used.
- Multiple imputation: The MCMC method will be used to impute intermittent missing data. The resulting multiply imputed data sets will be monotone missing and will be imputed using monotone regression (assuming a MAR pattern). Note that the multiple imputation procedure will be done on the continuous ASDAS variable, which will be dichotomized for the logistic regression analysis. ASDAS data collected after the discontinuation of double-blind study treatment will be treated as missing in the original data set for this sensitivity analysis and hence will not be used for analysis or imputing values.
- Tipping point analysis: In this analysis, various assumptions will be made about average outcomes among the subsets of subjects who prematurely discontinued double-blind study treatment. Various "delta adjustments" will be made to the assumed responses among missing data in each treatment arm with varying degrees of plausibility (O'Kelly, 2014). The goal of the tipping point analysis is to identify assumptions about the missing data under which the conclusions change, i.e., under which there is no longer evidence of a treatment effect. Then, the plausibility of such assumptions would be discussed. Further details of this procedure are described in Section 8.1.3.3.
- Observed case analysis: This analysis will only include the observed data for subjects still on the original double-blind study treatment. Data collected after the discontinuation of double-blind study treatment and all other missing data will be excluded from the analysis. The same logistic regression model specified for the primary efficacy analysis will be performed.

For Canada (and any other country where applicable or where requested by Regulatory Authorities), the primary efficacy variable is ASAS40 at Week 12 instead of ASDAS-MI at Week 52. For this reason, the above analyses will be repeated for ASAS40 at Week 12 with the composite endpoint analysis being the primary analyses.

4.2.2 Secondary efficacy variables

ASAS40 at Week 12, although a secondary efficacy variable for the USA, is described within Section 4.2.1 due to its status as a primary efficacy variable in other parts of the world.

The primary analysis method for the binary secondary efficacy variable(s), ASAS40 at Week 52, will be the same as that described above for the primary efficacy variable, ASDAS-MI. That is, a subject will be considered a responder only if the double-blind treatment course is completed and if ASAS40 is achieved. The sensitivity analyses of the secondary binary efficacy variable(s) (ASAS40 at Week 52 as described in Section 8.2) will be as follows:

- Including observed data at Week 52 (or Week 12 as applicable): As described for the primary efficacy variable.
- Multiple imputation: As described for the primary efficacy variable. Note that as ASAS40 is a composite of 4 different variables, the multiple imputation procedure will be performed on each of these components, and the ASAS40 response will be derived based on the multiply imputed datasets.
- Reference-based multiple imputation: This procedure will impute missing data as well as data collected at time points after the discontinuation of the double-blind study treatment for both the CZP and placebo groups. This procedure will use an imputation model developed based on data from the placebo group (Mallinckrodt, 2013). The estimand being evaluated in this case is the difference in the outcome of improvement in all randomized subjects at the planned endpoint, attributable to the initially randomized medication, which has been referred to as "estimand 6" (Mallinckrodt, 2012).
- Observed case analysis: As described for the primary efficacy variable.

For the continuous secondary efficacy variables (BASFI and BASDAI at Week 52 and 12, and SI joint SPARCC score at Week 12), the primary analysis method will be based on a referenced based multiple imputation procedure (details described in Section 8.2). The following sensitivity analyses will also be performed.

- Including observed data at Week 52 (or Week 12 as applicable): As described for the primary efficacy variable
- Multiple imputation: As described for the primary efficacy variable.
- Observed case analysis: As described for the primary efficacy variable
- Last Observation Carried Forward (LOCF): If there is missing data at the double-blind time point of interest, the last available post-Baseline measurement will be carried forward to that time point (including any previous scheduled or unscheduled visits in double-blind or open-label periods). Using the date that the observation was recorded, data will be carried forward to all missing double-blind visits up until the time point of interest even if the subject has withdrawn from the study or entered the open-label period. For example, a subject withdrawing from double-blind at Visit 14 /Week 24 and entering OL-CZP will proceed to have a open-label visits at weeks 0, 2 and 4 post double-blind withdrawal followed by assessments every 12 weeks until 52 weeks post randomization. Using the date of the open-label visits, the number of weeks post randomization will be calculated to allow data to be carried forward to all subsequent missing double-blind visits. This will not apply for the

analysis of SI joint SPARCC score at Week 12 since there are no measurements collected between Baseline and Week 12.

There will be no imputation or other method for handling missing data for the secondary efficacy variable, number of subjects without relevant changes to background medication. Further details on the derivation and analysis of this variable are described in Section 8.2.

4.2.3 Other efficacy variables

Analyses of other binary efficacy variables will be treated in the same way as the primary analysis of the primary efficacy variable. That is, a subject will be considered a responder only if the response is achieved and if the subject is still on their randomized double-blind study treatment at the time when the variable is evaluated. Analyses of other continuous efficacy variables will be based on LOCF. A sensitivity analyses will be performed on all other efficacy variables using observed case analysis as described for the primary endpoint in Section 4.2.1.

4.2.4 Safety variables

For analyses of AEs and concomitant medication usage, a complete date must be established in order to correctly identify the AE or medication as occurring during treatment or not. If time of study treatment and time of event or concomitant medication is available and non partial then it will also be used however if missing or partial, only the dates will be compared. For purposes of imputing missing components of partially-reported start and stop dates for AEs and for medication use, the algorithms listed below will be followed. Start and stop dates of AEs or concomitant medication will be displayed as reported in the subject data listings (i.e., no imputed values will be displayed in data listings).

- Missing start day, but month and year present:

  If the start of double-blind study medication occurred in the same month and year as the occurrence of the AE/concomitant medication, the start day of the event/concomitant medication will be assigned to the day of first administration of study medication during the double-blind period. Otherwise the start day will be set to the 1st day of the month.

- Missing start day and month, but year present:

  If the start of double-blind study medication occurred in the same year as the occurrence of the AE/concomitant medication, the start day and month will be assigned to the date of first administration of double-blind study medication. Otherwise the start day and month will be set to January 1st.

- Missing end day, but month and year present:

  The end day will be set to the last day of the month.

- Missing end day and month, but year present:

  If the maximum of the subject's date of study termination or the date equivalent to 70 days after the subject's last administration of study medication is the same year as the occurrence of the AE/Concomitant medication, then the end day and month will be set to the maximum of the date of study termination or the date equivalent to 70 days after last administration of study medication. Otherwise the end day will be set to December 31st of the given year.

4.2.5 Other considerations

Descriptive summaries for all efficacy variables based on observed case data (including only subjects still on their randomized double-blind study treatment) will also be prepared.

4.3 Interim analyses and data monitoring

An interim analysis is planned after the completion of the double-blind period of the last subject at Week 52. The timing of the analysis will be when the last subject completes Week 52 visit in accordance with the double-blind, OL-CZP or OL-OT schedule. At this time, all visit based data from the double-blind period up to and including Week 52 visit, all open-label visit based data up to Week 52 visit, all available Follow-up data for patients already completing the study, all hospitalization/emergency room visit and health care provider consultation data, all study medication discontinuation and all prior and concomitant medication data including concomitant medical procedures, will be locked. Subjects still on the study awaiting Follow-up visit or in SFE, will continue to have AEs, laboratory, vital sign, PK and physical examination data collected per schedule until completion of the Follow-up or SFE period, at which point they will complete the study termination eCRF page. At the time of the interim analysis Week 52 DB lock, adverse event data entered to date will be cleaned but not locked. This will allow ongoing adverse event entry during the Follow-up and SFE periods. The treatment codes will be made available to the study reporting team and an interim study report will be written. All tables, listings and figures described in this SAP will be produced at the time of the Week 52 DB lock. The Investigators and subjects will remain blind to the assigned CZP dose regimen of the double-blind period.

After the last subject has completed the SFE period, the database will be fully locked, and a final study report will be written. For subjects in the SFE period, from the Week 52 visit onward, subjects will be treated with OL-CZP until the last dosing visit of the study (SFE Week 104). During this time, only adverse events, concomitant medication related to adverse events, and study drug dispensation information will be collected in addition to the study termination data at completion or early withdrawal. Therefore, at the final DB lock, only the following tables and listings will be produced.

- Table 1.1.2: Disposition of Subjects Screened
- Table 1.2.2: Number of Subjects Completing each Visit
- Table 1.3: Disposition of Analysis Sets
- Table 1.4: Important Protocol Deviations
- Table 7.1: Extent of Exposure
- All tables in section 8 (adverse events, 31 tables in total with the exception of tables counting AEs reported after starting a new biologic, changing NSAIDs, changing DMARDs, or adding oral corticosteroids).
- Listing 1.2: Subject Disposition
- Listing 1.3: Study Termination
- Listing 1.4: Visit Dates

- Listing 3.1: Important Protocol Deviations
- Listing 4.1: Subject Analysis Sets
- All listings in section 7 (adverse events, 6 listings in total)

Note that if a substantial number of subjects are still awaiting their Follow-up visit when the interim analysis Week 52 DB lock occurs (and are therefore not entering the SFE), vital sign, laboratory, PK and physical examination outputs may be updated prior to the SFE analysis to include the information collected at the Follow-up visit.

Regular monitoring of safety data collected during the study will be performed as described in the Safety Signal Detection in the Ongoing Clinical Trials Charter for CZP.

A specific data monitoring-, steering-, or evaluation-committee is not planned for this study.

4.4 Multicenter studies

Due to the low number of subjects expected to be recruited per site, results will not be tabulated by individual sites. However important protocol deviations will be tabulated by region and the number of subjects randomized per region will also be presented. Listings will show the region and site for each subject. In addition, as subject randomization is stratified by region, efficacy analyses models will include region as a factor as described in Section 8.

4.5 Multiple comparisons/multiplicity

The statistical analysis of the primary efficacy variable and selected secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure. Further details on how the hierarchical testing will be implemented is provided in Section 8.

4.6 Use of an efficacy subset of subjects

The PPS will be used to evaluate subjects who have efficacy data during the double-blind treatment period and are reasonably compliant with the conditions of the study. This analysis set will provide additional information on the efficacy analysis and will describe findings in a subset of subjects who more closely follow the intentions of the study protocol.

The Randomized Set will be used to evaluate all subjects who were randomized to double-blind study medication. This analysis set will provide additional information on the efficacy analysis by describing findings in the full set of subjects who were randomized and will not exclude those who did not receive at least 1 dose of study medication or did not have a valid Baseline efficacy measurement for ASDAS.

Other than the planned sensitivity analyses based on the PPS and Randomized Set, no other efficacy subsets are defined for statistical analyses.

4.7 Active-control studies intended to show equivalence

Not applicable.

4.8 Examination of subgroups

Subgroups for age (18 – < 45 years, >=45 years), gender (male, female), race (white, other), symptom duration (<5, ≥ 5 years), tobacco use (never, current former), HLA-B27 genotype (positive, negative), region (North America, Europe, Asia), prior anti-TNF exposure (yes, no),

Baseline SPARCC score (<5, ≥5 as observed in the 2nd reading session or in the 1st if the 2nd reading is not available), subjects with/without relevant changes to background medication, , and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) will be utilized for summarizing the primary efficacy variable. Only summary statistics, estimates and confidence intervals will be presented and subjects with missing category will be excluded.

It is possible, that classification errors may occur within the randomization where a subject is found to have been randomized according to the wrong MRI/CRP strata when their MRI data and CRP results are re-examined post randomization. For this reason, the MRI/CRP classification, which will be used in all analyses and subgroup analyses will be one recalculated using the Screening MRI results and second Screening visits CRP results (3 to 5 days prior to Baseline). If the CRP result from the second screening visit is missing, available results from the first screening visit will be used.

Subjects will be categorized as MRI + if they have active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA as determined by the central readers. Otherwise they will be classed as MRI -.

Subjects will be categorized as CRP+ if their second Screening visit CRP result is >ULN. CRP values ≤ ULN will be considered CRP-. If the CRP result from the second screening visit is missing, available results from the first screening visit will be used. In the unlikely event that a subject has an unavailable recorded CRP result pre Baseline, they will be considered CRP+ for analyses of efficacy but missing for other CRP summaries.

Based on these definitions, the analysis variable for MRI/CRP classification will have the following 3 levels:

- MRI+/CRP+
- MRI+/CRP-
- MRI-/CRP+

Any subjects found to be MRI-/CRP- will have their MRI and CRP data examined to see which of the category thresholds they were close to. The subject will still be included in the FAS analyses however they will be assigned into the respective positive category (MRI+/CRP+, MRI+/CRP- or MRI-/CRP+) that they were closest to and documented to have failed inclusion criterion #9. Hence, they will be excluded from per protocol analyses.

Symptom duration will be categorized into <5 and ≥5 years for subgroup analyses and calculated as:

Start date of symptoms – date of first study medication administration

The start date of symptoms will be found using the medical history of the subject using the following rules (including imputation of partial dates as described in Section 4.2.4):

- Subjects with a medical history preferred term of ‘Back pain’ or ‘Inflammatory pain’ will use the earliest start date of these symptoms as the start date of symptoms.
- Otherwise, subjects with a preferred term of ‘Axial spondyloarthritis’ will use the earliest start date of disease as the start date of symptoms

- Otherwise, the subject's medical history will be reviewed in the DEM meeting to determine if the subject has evidence of a start date of symptoms or primary disease.
- Otherwise, the median duration of subjects with a valid symptom duration within the same stratum regarding MRI/CRP classification, will be used as the symptom duration of the subject, unless the duration is <3 months in which case 3 months and 1 day will be used.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number of subjects screened, and reason for screen failure will be summarized for all screened subjects. The disposition of screened subjects will also be presented including the date of the first and last subject into the study by region and site and number of subjects in each population by region and site.

The number of subjects randomized, completed Visit 28/Week 52, entered SFE, completed SFE, prematurely discontinued double-blind study treatment, prematurely discontinued from the study (by phase [main/SFE] and period [DB/OL-CZP/OL-OT]), and reason for premature discontinuation of study treatment and phase (main/SFE) will be summarized by treatment group. The number of subjects who complete each visit (as captured in the eCRF) will also be summarized. In addition, the number of subjects in each of the analysis sets, as specified in Section 3.5, will be summarized as well.

5.2 Protocol deviations

The process for reviewing and identifying important protocol deviations is outlined in Section 3.4. The number of subjects with at least one important protocol deviation will be summarized by treatment group in addition to whether that protocol deviation led to exclusion from the PPS.

The subject data listing, in contrast to the general approach (i.e., sorted by treatment group, region, site, subject number), will be sorted by region, site, treatment group, and subject number.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

The demographics and other Baseline characteristics will be presented for the RS. If the RS differs from the SS or the FAS, then demographics and Baseline characteristics tables may be repeated separately for these analysis sets. These summaries will be presented by treatment group and all subjects.

Tables on medical history and prior diseases, and concomitant and prior medications will also be presented.

6.1 Demographics

The following continuous demographic variables will be summarized:

- Age (years)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

The following categorical demographic variables will also be summarized:

- Gender (Female, Male),
- Race (American Indian / Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Other / Mixed),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino),
- Racial subgroup (White, Other),
- Age class (to be summarized 3 ways: 1) 18-<65, 65-<85 and >=85; 2) ≤18, >18 to <65 years, and ≥65 years; and 3) 18 – <45 years, 45 – <65 years, ≥65 years),
- BMI class (<18.5 kg/m^2, 18.5 kg/m^2 to <25 kg/m^2, 25 kg/m^2 to <30 kg/m^2, ≥30 kg/m^2)

6.2 Other Baseline characteristics

In this section, the variables that will be summarized as Baseline characteristic are described.

The different binary items of the ASAS criteria will be presented in frequency tables:

- back pain of ≥ 3 month duration and age of onset < 45 (and per inclusion criteria back pain of ≥ 12 month duration and age of onset < 45)
- active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- HLA-B27 positivity (current features)
- inflammatory back pain (history and current features)
- arthritis (history and current features)
- enthesitis (history and current features)
- uveitis (history and current features)
- dactylitis (history and current features)
- psoriasis (history and current features)
- Crohn's disease/ ulcerative colitis (history and current features)
- elevated CRP (history and current features)

Symptom duration (calculated as described in Section 4.8) and time since diagnosis of disease will be summarized as continuous variables and dichotomized into <5 years and ≥5 years. Time since diagnosis of disease will be defined as: Earliest start date of the medical history (lower level term) of Axial Spondyloarthritis – date of first study medication administration. If a subject does not have a history of 'Axial Spondyloarthritis', then the time since diagnosis of disease will be set equal to the symptom duration.

Frequency tables will be provided for the following Baseline variables related to TB status:

- Contact with an individual with active TB
- Contact with an individual who has recently been treated for TB

Summary statistics will be provided for the laboratory variable CRP. Additionally, CRP at Baseline will be categorized based on the number of subjects with CRP ≤ULN and >ULN at Baseline.

Frequency tables will summarize HLA-B27, the test at Screening to rule out hepatitis B surface antigen, and the test at Screening to rule out antibodies to hepatitis C.

Frequencies will also be provided for subjects with the following:

- Peripheral arthritis (swollen joint count > 0) at Baseline
- Enthesitis (MASES > 0)
- Extra-articular manifestations:
  - History of uveitis
  - History of psoriasis
  - History of IBD
- Concomitant DMARDs at Baseline
- Prior DMARDs and prior NSAIDs
- MRI/CRP classification (presented as used for stratification at IXRS randomization and as found in the source data along with a cross tabulation to display the number of misclassifications):
  - MRI+/CRP+
  - MRI+/CRP-
  - MRI-/CRP+
- Baseline cardiovascular risk elements (such as smoking, caffeine, and alcohol use)

Note that the term DMARDs is used above as it is common to rheumatic diseases. However, there is currently no conclusive evidence that DMARDs are in fact disease-modifying in axSpA (unlike in RA). As a result, the term SAARDs (slow-acting anti-rheumatic drugs) is used in the protocol to refer to this class of medications. The DMARDs terminology is generally used in this SAP, but it is recognized that SAARDs may be more appropriate in the context of a study of subjects with axSpA.

Since the procedures and surgeries in the procedural history will not be coded, these data will only be presented in listings.

Baseline information for other key measures related to axSpA (eg, BASFI, BASDAI, BASMI, and ASDAS) will be presented in the respective tables providing descriptive statistics over time.

6.3 Medical history and concomitant diseases

Previous and ongoing medical history will be summarized by MedDRA® system organ class (SOC) and preferred term (PT). Medical procedures are not coded. Concomitant diseases will be recorded by the Investigator at the Screening visit only.

6.4 Prior and concomitant medications

Prior medications include any medications that started prior to the start date of double-blind study medication. Past medications are a subset of prior medications, and include prior medications with a stop date before the date of first double-blind study medication administration.

Concomitant medications will be assigned to treatments according to whether they were taken at least one day in common with the treatment dosing period of that treatment as described in Table 6–1. Dosing periods are defined as follows:

- For double-blind period: From first administration of double-blind medication to last administration of double-blind medication +14 days or first administration of open-label CZP, open-label other treatment or SFE period treatment, whatever comes first.
- For open-label CZP period: From first administration of open-label CZP medication to last administration of open-label CZP medication +14 days or first administration of open-label other treatment or SFE period treatment, whatever comes first.
- For open-label other treatment period: From first administration of open-label other treatment medication to last administration of open-label other treatment medication.
- For SFE period: From first administration of SFE period treatment to last administration of SFE period treatment + 14 days.

A medication can be defined as both prior and concomitant and can be concomitant to more than one treatment. Where a medication start or stop date is (partially) missing, the medication will be considered a concomitant medication, if there is the possibility of concomitant use according to the rules described in Section 4.2.4. Hence, if a partial date implies the concomitant medication could have been taken concomitant to multiple treatments, , it will be concomitant to all applicable treatments.

Table 6–1: Assignment of Concomitant Medications to treatments		
Period	Description	Treatment
Double-blind treatment	1) If the start or end date of the concomitant medication falls into the double-blind dosing period or 2) if the concomitant medication starts prior to double-blind dosing period and ends after the double-blind dosing period or is ongoing, then assign to the double-blind treatment.	Summarized according to randomized CZP 200mg Q2W or PBO. For subjects randomized to CZP 200mg Q2W, also include the medications in Total CZP incl DB and OL. All double-blind period medications will be included in an All subjects summary.
Open-label CZP treatment	1) If the start or end date of the concomitant medication falls into the OL-CZP dosing period or 2) if the concomitant medication starts prior to the OL-CZP dosing period and ends after the OL-CZP dosing period or is ongoing, then assign to the OL- CZP treatment.	Summarized according to CZP 200mg Q2W or PBO followed by open-label CZP (i.e. CZP->OL CZP or PBO->OL CZP). All open-label CZP period medications will also be included in a Total CZP incl DB and OL and an All subjects summary.
Open-label other treatment (OL-OT)	1) If the start or end date of the concomitant medication falls into the OL-OT dosing period or 2) if the concomitant medication starts prior to the OL-OT dosing period and ends after the OL-OT dosing period or is ongoing, then assign to the OL-OT.	Only included in an All subjects summary.
Safety Follow-up Extension treatment	If the start date of the concomitant medication falls into the SFE dosing period then assign to the SFE treatment. **Note:** Concomitant medication information is not systematically recorded during the SFE period. Only concomitant medication taken due to an adverse event will be documented in the CRF during that period. Only new medication starting during the SFE dosing period will therefore be considered.	Not summarized in tables

If a medication starts on the start date of a new dosing period, it will be considered concomitant to the treatment of that new period, but not to the treatment of the previous dosing period (even if the end date of the corresponding dosing period is on the same day as the start of the new dosing period.).

If a medication stops on the start date of a new dosing period it will not be considered concomitant to the treatment of that new dosing period, unless start and stop date of the medication are on the same date.

Past medication summaries will be generated for DMARDs, NSAIDs, and Anti-TNFs by ATC code (level 3 (4-digit) decode, level 4 (5-digit) decode, and Preferred Term).

Prior DMARDs and NSAIDs will be summarized by WHO-DRL ATC code (level 3 (4-digit) decode, level 4 (5-digit) decode, and Preferred Term). No extra table for prior Anti-TNFs will be produced due to the fact that this summary is identical to the 1 for the past Anti-TNF.

Prior medication (except DMARDs and NSAIDs) will be summarized by WHO-DRL ATC code (level 2 (3-digit) and level 3 (4-digit) decode.

Concomitant DMARDs and NSAIDs will be summarized by WHO-DRL ATC code (level 3 (4-digit) decode, level 4 (5-digit) decode, and Preferred Term).

Concomitant medication (except DMARDs and NSAIDs) will be summarized by WHO-DRL ATC code (level 2 (3-digit) and level 3 (4-digit) decode.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

All described calculations of treatment compliance will correspond to double-blind study medication only.

There will be 2 approaches to calculate treatment compliance. The first will utilize the number of administered syringes and compare them to the scheduled expected number of injections. Two syringes will be dispensed in each kit. Both syringes should be administered for the loading doses (at weeks 0, 2 and 4) however only 1 syringe should be administered at any other visit. The difference in number of syringes between the total actual used and the total expected syringes will be summarized. For calculation of total expected syringes, all scheduled administration up to and including the last administration prior to switch to open-label CZP / other treatment or start of SFE treatment will be considered, assuming a 14 days dosing interval. If a subject continues to take double-blind medication after week 52 and prior to start of SFE following instructions from the sites, such administrations will also be included as expected syringes in the calculation.

In addition, a ratio of compliance will be further computed based on the number of actual and expected syringes. The ratio of compliance will be summarized as a continuous variable and categorically (<0.80, ≥0.80-≤1.0, >1.0-<=1.2 and >1.2). The general formula for the compliance ratio (CR) is given as follows:

CR for syringes = # actual syringes / # expected syringes

The second approach defines compliance with study drug administration based upon comparing the actual day of administration with the expected day of administration. The expected day of administration will be based upon the Baseline date. The sum of the absolute difference in days between the actual and expected days will be summarized. In addition, a ratio of compliance will be further computed based upon the actual and expected day. The ratio of compliance will also be summarized as a continuous variable and categorically (<0.80, ≥0.80-≤1.0). The general formula for the compliance ratio is given as follows:

CR for injection day = (DB Study Duration - Cumulative Difference) / DB Study Duration

The CR for injection day ranges between 0 and 1.

To calculate double-blind study duration, the date of the last injection date prior to double-blind study treatment discontinuation will be compared to the Baseline date, as shown below:

Double-blind Study Duration (days) = last DB injection date – Baseline date (maximum value is 350 days)

Cumulative Difference (days) = sum (ABS [actual date – scheduled date])

The sum will be calculated for the 26 visits from Week 0 (Baseline) to Week 50.

In case the actual day of administration is missing, the maximum deviation to the scheduled day will be assumed (ie, 14 days). If, for a scheduled day with 2 planned injections, the syringes were administered on 2 different days, the maximum day difference of the 2 actual dates to the scheduled date will be utilized.

8 EFFICACY ANALYSES

All efficacy analyses will be performed using the FAS. The PPS and Randomized Set will be used for a sensitivity analysis on the primary endpoint only (using the composite endpoint analysis).

The statistical analysis of the primary efficacy variable and selected secondary efficacy variables will account for multiplicity by using a fixed sequence testing procedure. The predefined order of hypotheses testing, each at a 2-sided 0.05 significance level for the comparison between CZP 200mg Q2W and placebo, will be performed in the sequence shown below. After the first test, each subsequent test is performed only if the previous test is significant in favor of CZP at the 2-sided 0.05 level. Note that the first test relates to the primary efficacy variable while the others provide the sequential testing for selected secondary efficacy variables:

Primary:

1. ASDAS-MI response at Week 52 (Composite endpoint analysis)

Secondary:

2. ASAS40 response at Week 12 (Composite endpoint analysis)
3. Change from Baseline in BASDAI at Week 12 (Reference based multiple imputation analysis)
4. Change from Baseline in BASFI at Week 12 (Reference based multiple imputation analysis)
5. ASAS40 response at Week 52 (Composite endpoint analysis)
6. Change from Baseline in BASDAI at Week 52 (Reference based multiple imputation analysis)
7. Change from Baseline in BASFI at Week 52 (Reference based multiple imputation analysis)
8. Change from Baseline in SI joint SPARCC score at Week 12 (Reference based multiple imputation analysis)
9. Change from Baseline in ASQoL at Week 52 (Reference based multiple imputation analysis)
10. Change from Baseline in nocturnal spinal pain (NRS) at Week 52 (Reference based multiple imputation analysis)
11. Number of subjects with AU or new AU flares through Week 52

Hierarchical testing of efficacy variables for Canada (and any other country where applicable or where requested by Regulatory Authorities):

Primary:

1. ASAS40 response at Week 12 (Composite endpoint analysis)

Secondary:

2. ASDAS-MI response at Week 52 (Composite endpoint analysis)
3. Change from Baseline in BASDAI at Week 12 (Reference based multiple imputation analysis)
4. Change from Baseline in BASFI at Week 12 (Reference based multiple imputation analysis)
5. ASAS40 response at Week 52 (Composite endpoint analysis)
6. Change from Baseline in BASDAI at Week 52 (Reference based multiple imputation analysis)
7. Change from Baseline in BASFI at Week 52 (Reference based multiple imputation analysis)
8. Change from Baseline in SI joint SPARCC score at Week 12 (Reference based multiple imputation analysis)
9. Change from Baseline in ASQoL at Week 52 (Reference based multiple imputation analysis)
10. Change from Baseline in nocturnal spinal pain (NRS) at Week 52 (Reference based multiple imputation analysis)
11. Number of subjects with AU or new AU flares through Week 52

The approach for handling missing values is described in Section 4.2.

The primary analyses to be used in the fixed sequence testing procedure are described in Sections 8.1 and Section 8.2. Further sensitivity analysis and various approaches for handling missing data values are described in Section 4.2.

8.1 Statistical analysis of the primary efficacy variable

The primary efficacy variable measurement for this study is based on ASDAS-MI response at Week 52. However, the primary outcome of the study will be defined as a composite endpoint that is achieved if a subject fulfills the following 2 components:

1. Remain in the study and on the double-blind study treatment through 52 weeks
2. Achieve an ASDAS-MI response at 52 weeks

For simplicity, this primary efficacy variable will be referred to as ASDAS-MI response at Week 52. However, the composite definition as described above will apply when this endpoint is analyzed.

8.1.1 Derivation of primary efficacy variable

The ASDAS is comprised of a number of assessments which are scored by the subject and physician and multiplied by a proven formula (van der Heijde et al, 2008) as listed:

- 0.121 x Back pain (BASDAI Q2 result)
- 0.058 x Duration of morning stiffness (BASDAI Q6 result)
- 0.110 x Patient's Global Assessment of Disease Activity (PGADA)
- 0.073 x Peripheral pain/swelling (BASDAI Q3 result)
- 0.579 x (natural logarithm of the (CRP [mg/L]+ 1))

Back pain, PGADA, duration of morning stiffness, peripheral pain/swelling and fatigue are all assessed on a numerical scale (0 to 10 units) (Lukas et al, 2009).

The sum of these weighted components gives the ASDAS.

If exactly 1 component for the ASDAS is missing at a given visit, that component will be imputed by LOCF, and the ASDAS will be calculated accordingly. If more than one component for the ASDAS is missing, ASDAS will be treated as missing.

For CRP values below the lower limit of quantification (<4mg/L), half the lower limit (2mg/L) will be used as the imputed value.

Disease activity categories based on ASDAS are as follows:

- ASDAS-Inactive Disease (ASDAS-ID): ASDAS <1.3
- ASDAS-Moderate Disease (ASDAS-MD): ASDAS >=1.3, <2.1
- ASDAS-High Disease Activity (ASDAS-HD): ASDAS >=2.1, <=3.5
- ASDAS-very High Disease Activity (ASDAS-vHD): ASDAS >3.5

The variables related to ASDAS improvement are defined as follows:

- ASDAS-Clinically Important Improvement (ASDAS-CII): ASDAS reduction (improvement) of >=1.1 relative to Baseline
- ASDAS-Major Improvement (ASDAS-MI): ASDAS reduction (improvement) of >=2.0 relative to Baseline or has the lowest score possible post-baseline (i.e. when CRP<LLOQ and all other components are 0, then the minimum ASDAS score is 0.636 to 3 decimal places). Note: As a sensitivity analysis, the primary analysis will be repeated where ASDAS-MI includes the criteria ASDAS reduction (improvement) of >=2.0 relative to Baseline only.

ASDAS-MI at 52 weeks is the primary variable for efficacy analysis.

8.1.2 Primary analysis of the primary efficacy variable

The primary analysis for of the primary efficacy variable will be based on logistic regression. The odds ratio of the ASDAS-MI responder rates at Week 52 will be estimated and tested between treatment groups using a logistic regression model with factors of treatment group, region, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+). The MRI/CRP classification used in all statistical analysis will be recalculated using source data as described in

Section 4.8 and the IXRS MRI/CRP categorization will not be used. If the logistic regression model is unable to converge, then the MRI/CRP classification variable may be dropped from the model to facilitate convergence. The study design is likely to result in some sites with a small number of enrolled subjects. The use of region as a factor in the model is intended to combine study centers in similar geographic regions. The geographic regions to be used will be as defined in the IXRS randomization system. In the unlikely event that a subject moves sites during the study which leads to a change in region, the region originally used at randomization will be used in the analysis.

Given the composite endpoint definition described in Section 8.1, there will be no missing data for the primary endpoint, as subjects that discontinue double-blind study treatment prior to Week 52 or who do not have an ASDAS-MI response at Week 52 are considered non-responders to the double-blind study treatment.

Tables will present the responder rates for placebo and CZP 200mg, the respective effect estimates (adjusted odds ratio with reference to placebo), p-values, and 95% confidence intervals (CIs). The odds ratios and 95% CIs will also be presented graphically.

8.1.3 Supportive and sensitivity analyses of the primary efficacy variable

As described in Section 6.3 of the protocol, subjects who discontinue study treatment will not necessarily be withdrawn from the study. In an attempt to minimize missing data, efforts will be made to continue to collect safety and efficacy data on these subjects through study completion. In order to assess the impact of various missing data assumptions on the analysis, four sensitivity analyses of the primary efficacy variable will be performed as described in Section 4.2.1. Further details of these analyses are provided in this section. The odds ratios ± 95% CI's for the primary analyses and sensitivity analyses will be presented on the same graph to allow visual comparison of the robustness of the results. In addition, a summary of the missing data pattern will be provided.

For Canada (and any other country where applicable or where requested by Regulatory Authorities), the primary efficacy variable measurement is the ASAS40 response at Week 12. Analysis of the ASAS40 response at Week 12 will be performed as described above for ASDAS-MI response at Week 52 (including all sensitivity and subgroup analyses). Similar to the ASADAS-MI efficacy endpoint, the primary analysis of ASAS40 will be treated as a composite endpoint when it is analyzed. Specifically, subjects will need to: 1) achieve the relevant response (ASAS40); and 2) remain in the study and on their randomized double-blind study treatment through Week 12.

In addition to the above analyses, subgroup summaries using descriptive statistics, estimates and confidence intervals only for the primary efficacy variable by age, gender, race, symptom duration, tobacco use, HLA-B27 genotype, region, prior anti-TNF exposure, Baseline SPARCC score (<5, ≥5), subjects with/without relevant changes to background medication, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) will be performed.

The logistic regression analyses of the composite endpoint for ASDAS-MI responder rates at Week 52 (as described in Section 8.1.2) will also be repeated using the PPS and the Randomized Set. In addition, the primary analysis will be repeated where ASDAS-MI includes the criteria ASDAS reduction (improvement) of >=2.0 relative to Baseline only.

8.1.3.1 Including observed data at Week 52

The observed data at Week 52 will be used and analyzed according to randomized treatment, regardless of whether or not the subject is still on his/her randomized double-blind study treatment at that time. For example, subjects on OL-CZP or OL-OT at the time of their Week 52 visit will have that data included in the analysis including observed data at Week 52. Despite efforts to continue to collect data on all subjects (even if they discontinue the double-blind study treatment), there may still be subjects with missing data at Week 52. Such subjects will be considered as non-responders. The same logistic regression model specified for the primary analysis will be used. The odds ratio of the treatment comparison and corresponding 95% CI for ASDAS-MI responder rates at Week 52 based on the observed data will be estimated using a logistic regression model with factors of treatment group, region, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+).

8.1.3.2 Multiple imputation

Investigators will be given discretion to discontinue study treatment for subjects not responding in order to provide them with other treatments for the condition. Therefore, in many cases, missing efficacy data due to study treatment discontinuation should be dependent on the observed efficacy scores, but independent of unobserved data. This would be consistent with a missing at random (MAR) pattern of missingness. In order to investigate the efficacy results under the assumption of data being MAR, a multiple imputation method will be applied as follows:

1. The continuous ASDAS score at each visit will be calculated using the methods described in Section 8.1.1 (including the application of LOCF if only one component is missing). Visits with more than one component missing will be set to missing. ASDAS data collected after the discontinuation of double-blind study treatment will be treated as missing in the original data set for this sensitivity analysis. Hence, all open-label period data is excluded from this analysis.
2. For subjects with a non-monotone (intermittent) missing pattern, MCMC will be used to impute their missing intermittent ASDAS scores including treatment arm, region, MRI/CRP classification and ASDAS measurement from previous visit(s) as explanatory variables in the model. This will be done 100 times limiting the imputation to in range results.

   After this step there will be 100 datasets containing all subjects however the only missing data will be a monotone missing data pattern. A variable called "_imputation_" will identify each of the 100 imputed datasets output.
3. The remaining missing data for all subjects with a monotone missing data pattern will be imputed using regression with treatment arm, region, MRI/CRP classification and ASDAS measurement from previous visit(s) as explanatory variables. This model will be run once for each of the imputed datasets limiting imputation to in range results.
4. The ASDAS change from Baseline to Week 52 will be calculated using the complete datasets (with no missing data) and categorized as: ASDAS-MI or not ASDAS-MI (as defined in Section 8.1.1)
5. For each of the 100 imputed datasets (identified by _imputation_ variable), the odds ratio of the treatment comparison and corresponding 95% CI for ASDAS-MI responder rates at

Week 52 based on the observed data will be estimated using a logistic regression model with factors of treatment group, region, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) and Baseline as a covariate in the same manner as the primary endpoint analysis.

6. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

   The parameter estimate and 95% CIs will be back transformed (using the exponential function) to give the odds ratio and CI for the CZP vs PBO comparison. This will be presented alongside the p-value from the proc mianalyze.

8.1.3.3 Tipping point analysis

In this analysis, various assumptions will be made about average outcomes among the subsets of subjects who prematurely discontinued double-blind study treatment and hence have a monotone missing data pattern. Various "delta adjustments" will be made to the assumed responses among missing ASDAS data in each treatment arm with varying degrees of plausibility (O'Kelly, 2014) prior to classification of the composite endpoint ASDAS-MI. The goal of the tipping point analysis is to identify assumptions about the missing data under which the conclusions from the logistical regression change, i.e., under which there is no longer evidence of a treatment effect. Then, the plausibility of such assumptions will be discussed.

Since the tipping point analysis is to find out how much of a change is required to "tip" the result from statistically significant at the alpha=0.05 level to not statistically significant, it will not be performed if the primary endpoint analysis is not statistically significant (p-value <=0.05) at the onset.

1. Steps 1 and 2 from Section 8.1.3.2 will be completed followed by steps 2-6 as shown below. Note that as described in Section 8.1.3.2, part 1, ASDAS data collected after the discontinuation of double-blind study treatment will be treated as missing and then imputed using the methods described. Hence, all open-label period data is excluded from this analysis.

2. The remaining monotone missing data for all subjects will be imputed by treatment group. A regression with ASDAS measurement from the previous visit(s), MRI/CRP classification and region as explanatory variables will be used to impute the missing data including a MNAR mechanism under different assumptions. For subjects randomized to the Placebo treatment group, a MNAR mechanism will be assumed by using a specified negative shift to decrease the ASDAS parameter values prior to classifying the subject according to the ASDAS-MI endpoint. For subjects randomized to the CZP treatment group, a MNAR mechanism will be assumed by using specified positive shift parameters to increase imputed ASDAS values prior to classifying the subjects according to the ASDAS-MI endpoint. The size of the shift in the CZP or PBO treatment group will be investigated to determine at what point the analysis leads to a non-significant result.

   As it is the raw ASDAS scores being imputed, the shift size (delta) will start with 0, 0.1, 0.2, 0.3, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6 and 1.8. Further values for delta may be investigated depending on the results obtained in order to determine the point at which the results are no longer significant.

When tipping point analyses is applied to ASAS40 response, the imputation will be done on the raw components before assessing the imputed results for ASAS40 response. The same delta shifts (0, 0.1, 0.2, 0.3, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6 and 1.8) will be investigated applied to the raw components (each of which are on a scale from 0 to 10) prior to calculating ASAS40 response. Further values for delta may be investigated depending on the results obtained.

This will be done once for each of the 100 datasets. The same delta value will be assumed for all visits.

3. The ASDAS change from Baseline to Week 52 will be calculated using the complete datasets (with no missing data) and categorized as: ASDAS- MI or not ASDAS-MI.
4. For each of the 100 imputed datasets (identified by _imputation_ variable), the odds ratio of the treatment comparison and corresponding 95% CI for ASDAS-MI responder rates at Week 52 based on the observed data will be estimated using a logistic regression model with factors of treatment group, region, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) and Baseline as a covariate in the same manner as the primary endpoint analysis.
5. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE. The parameter estimate and 95% CIs will be back transformed (using the exponential function) to give the odds ratio and CI for the CZP vs PBO comparison. This will be presented alongside the p-value from the proc mianalyze.
6. Steps 2 through 5 will be repeated using different values for the shift parameter as specified in step 2. Following the final Step 5, for each value of delta, the odds ratios, CIs and p-values will be presented in a single table with the associated delta value which was applied in the analysis.

8.1.3.4 Observed case analysis

This analysis will only include the observed data for subjects still on the original double-blind study treatment. Subjects with missing ASDAS data at Week 52 will not be included in the analysis and hence only a subset of subjects will be analyzed and no composite endpoint implemented. The same logistic regression model specified for the primary efficacy analysis will be performed. The odds ratio and corresponding 95% CI of the ASDAS-MI responder rates at Week 52 based on the observed data will be estimated and tested between treatment groups using a logistic regression model with factors of treatment group, region, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+).

8.2 Statistical analysis of secondary efficacy variables

The secondary efficacy variables are designated as variables 2 through 11 in the hierarchical testing procedure outlined in Section 8, in addition to counts of relevant changes to background medication. The statistical methodology to be used for the analysis of these variables is described below.

8.2.1 Derivation of secondary efficacy variables

8.2.1.1 Assessment in Axial SpondyloArthritis international Society response criteria (ASAS20/40, ASAS5/6, and ASAS partial remission)

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 (Anderson, 2001):

- Patient's Global Assessment of Disease Activity;
- Pain assessment (the total spinal pain NRS score);
- Function (represented by the 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].

ASAS data collected after the discontinuation of double-blind study treatment will be treated as missing in the original data set.

The ASAS criteria for 40% improvement (ie, ASAS40) are defined as relative improvements of at least 40% and absolute improvement of at least 2 units on a 0 to 10 NRS in at least 3 of the 4 domains and no worsening at all in the remaining domain.

The ASAS 5/6 response is defined as at least 20% improvement in 5 of 6 domains, which includes spinal mobility (i.e., lateral spinal flexion of the BASMI) and CRP as more objective measures (Brandt et al, 2004). For CRP values below the lower limit of quantification (<4mg/L), half the lower limit (2 mg/L) will be used as the imputed value.

The ASAS partial remission response is defined as a score of ≤2 units on a 0 to 10 unit scale in all 4 domains.

ASAS40 response at Week 12 and Week 52 are secondary efficacy endpoints.

8.2.1.2 Bath Ankylosing Spondylitis Disease Index (BASDAI)

The BASDAI is the most commonly used instrument to measure the disease activity of ankylosing spondylitis. The BASDAI is a validated self-reported instrument which consists of 6 horizontal NRSs, each with 10 units to measure the severity of the 5 major symptoms: fatigue, spinal pain, peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration) over the last week. To give each symptom equal weighting, the average of the 2 scores relating to morning stiffness is taken. The resulting 0 to 50 sum score is divided by 5 to give a final BASDAI score between 0 and 10, with lower scores indicating lower disease activity.

If 1 of the 2 morning stiffness measurements (ie, questions: "[redacted]" and "[redacted]") is missing, the other one will be used for the morning stiffness calculation. The same imputation is also applied for the calculation of the ASAS inflammation component, which is calculated as the average of the 2 morning stiffness measurements.

If 1 major symptom of the BASDAI is missing, the sum score of the remaining symptoms will be divided by the number of symptoms assessed. If more than 1 major symptom is missing, the sum score will be set to missing.

The BASDAI data collected after the discontinuation of double-blind study treatment will be treated as missing in the original data set.

The BASDAI50 response is defined as an improvement of at least 50% in the BASDAI compared to Baseline.

Change from Baseline in BASDAI at Week 12 and Week 52 are secondary efficacy endpoints.

8.2.1.3 Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI contains 10 questions. The first 8 questions evaluate activities related to functional anatomical limitations due to the course of this inflammatory disease. The final 2 questions evaluate the subjects' ability to cope with everyday life. An NRS ranging from 0 to 10 is used to answer the questions on the test.

The mean of the 10 scales gives the BASFI score, which is a value between 0 and 10.

In case of missing answers to 1 or 2 of the single items within the BASFI questionnaire, the BASFI score will be calculated by imputing missing items with the mean of the completed items. Then, the BASFI score will be calculated as described above. If more than 2 of the items are missing, the BASFI score will be left missing.

The BASFI data collected after the discontinuation of double-blind study treatment will be treated as missing in the original data set.

Change from Baseline in BASFI at Week 12 and Week 52 are secondary efficacy endpoints.

8.2.1.4 Magnetic Resonance Imaging (MRI) assessments

The SPARCC scoring method for lesions found on the MRI is based on an abnormal increased signal on the short-tau-inversion recovery (STIR) sequence, representing bone marrow edema (defined as an increased signal in bone marrow on a T2-weighted sequence, reflecting an increased concentration of "free water" related to a bone lesion). Each SI joint is divided into 4 quadrants: upper iliac, lower iliac, upper sacral, and lower sacral. The presence of increased signal on STIR in each of these 4 quadrants is scored on a dichotomous basis, where 1 = increased signal and 0 = normal signal. Joints that include a lesion exhibiting intense signal are each given an additional score of 1 per slice that demonstrated this feature. Similarly, each joint that included a lesion demonstrating continuous increased signal of depth greater or equal 1 cm from the articular surface is also given an additional score of 1. The scoring is repeated in each of 6 consecutive coronal slices. Total SI joint SPARCC scores can range from 0 to 72.

The Berlin modification of the ASspiMRI-a is a scoring system with a concentration on STIR sequences without other fat saturation techniques. This scoring method quantifies active changes in 23 vertebral units (VU) of the spine (from C2 to S1). A VU is defined as the region between 2 virtual lines through the middle of each vertebra. Active inflammation is scored by grading the degree of bone marrow edema from 0 to 3 in 1 dimension on 1 or more consecutive slices that represent the highest level of inflammation in a particular VU. Total spine ASspiMRI-a score in the Berlin modification can range from 0 to 69.

The following imputation rules should be used for calculating the total for both SI joint SPARCC scores and spine ASspiMRI-a score in the Berlin modification:

- If all scores are NA at a visit, the imputed total is blank for that visit.
- Treat NA as 0 when computing the total score.
- Carry the NA score from the Baseline visit forward to all post-Baseline visits unless all scores at Baseline are NA.
- Carry the numeric score from the last visit with non-NA score forward if a score is NA at a post-Baseline visit (unless all scores are NA post-Baseline).
- If ALL the Baseline scores are NA, then do not carry forward the Baseline scores. Treat the subsequent visit as a surrogate Baseline.

The details related to how the MRI data will be read and adjudicated will be outlined in a separate imaging charter. In the cases where the initial two readings are discrepant, a third reading is performed by an independent reader. This third score is not an adjudication but rather an additional score and value for analysis which will be based on the average of all 3 reader assessments. There will also be two sessions of readings. The first session will conduct readings of the Baseline and Week 12 MRI and will be used for summaries at Week 12. The second session will conduct readings of the Baseline, Week 12 and Week 52 MRIs and will be used for summaries at Week 52.

The following visit windows will be applied:

- All Baseline values should be collected prior to randomization as MRI is required to be randomized into the study.
- For post-Baseline visits, a time window of 2 weeks before or after the scheduled visit will be used for mapping MRI data to the given visit.

The SI joint SPARCC data collected after the discontinuation of double-blind study treatment will be treated as missing for any observed case analysis.

The change from Baseline in SI joint SPARCC score at Week 12 is a secondary efficacy endpoint.

8.2.1.5 Relevant changes to background medication

For purposes of this secondary efficacy variable, relevant changes to background medication will be defined as the following:

- The addition of a new DMARD or the change from one DMARD to another
- The addition of an NSAID or the change from one NSAID to another
- Increased dose of chronic oral corticosteroids
- Increased dose in chronic analgesic medications or the addition of a chronic analgesic medication

The variable to be measured is the number of subjects without relevant changes to background medications. Therefore, a subject who does not have any of the above relevant changes made to background medication during the study through Week 52 will be considered to have met this

endpoint. Conversely, subjects who have one of the above relevant background medication changes or who do not complete double-blind study treatment to Week 52 will be considered as not having met this endpoint.

8.2.1.6 Ankylosing Spondylitis Quality of Life (ASQoL)

The ASQoL, a validated disease-specific 18-item questionnaire, has been developed specifically for measuring HRQoL in subjects with AS (Doward et al, 2003). An nr-axSpA specific scoring algorithm is presently being developed, but it is unclear when this algorithm will become available relative to the timing of the AS0006 database lock. Should this alternative scoring approach become available prior to finalization of the clinical study report, analyses of ASQoL data may be repeated using this alternate scoring approach appropriate for nr-axSpA population and methods will be described either in a SAP amendment or within the Documentation of Statistical Methods appendix to the study report.

8.2.1.7 Nocturnal Spinal Pain

Nocturnal spinal pain will be recorded based on a NRS ranging from 0 to 10, where 0 represents no pain and 10 represents most severe pain.

8.2.2 Primary analysis of the secondary efficacy variables

The comparison of CZP 200mg Q2W to placebo as described in this section for the ASAS40 response, BASDAI, and BASFI at Week 12 and Week 52, SI joint SPARCC score at Week 12, ASQoL at Week 52 and Nocturnal Spinal Pain at Week 52 will be part of the fixed sequence testing procedure outlined in Section 8.

8.2.2.1 Primary analysis of categorical secondary efficacy variables

The ASAS40 response at Week 12 and Week 52 are responder secondary efficacy variables. For Canada and any other country where applicable or where requested by Regulatory Authorities, the ASAS40 response at Week 12 is the primary efficacy variable; the ASAS40 response at Week 52 and the ASDAS-MI response at Week 52 are secondary efficacy variables. Hence the primary and sensitivity efficacy analysis on ASDAS-MI at Week 52 will be repeated for ASAS40 at Week 12.

As a responder variable, ASAS40 will be analyzed using logistic regression in the same manner as for the primary analysis described in Section 8.1.2. As with the primary efficacy variable, the ASAS40 will be treated as a composite endpoint when it is analyzed. Specifically, subjects will need to 1) achieve the relevant response (ASAS40) and 2) remain in the study and on their randomized double-blind study treatment through the time point being analyzed (Week 12 or Week 52).

Relevant changes to background medication will also be analyzed using the same composite endpoint logistic regression model described for the primary variable described in Section 8.1.2.

The number of subjects with new onset post-Baseline AU or new AU flares through Week 52 is a categorical secondary efficacy endpoint for all regions. Subjects will be classified as having post-Baseline Uveitis: a TEAE of Uveitis, a new diagnosis of Uveitis or a flare of uveitis at any visit post-Baseline which is on or before the Week 52 visit. All patients without evidence of uveitis events, new diagnosis or flares will be considered not to have post-Baseline Uveitis. As a dichotomous outcome variable, treatment groups will be compared for differences using logistic

regression including treatment, region and MRI/CRP classification as explanatory variables. Subjects with no evidence of new AU flares will be considered as having no flare.

8.2.2.2 Primary analysis of continuous secondary efficacy variables

The continuous BASDAI, BASFI, ASQoL and Nocturnal Spinal Pain score at each visit will be calculated using the methods described in Sections 8.2.1.2, 8.2.1.3, 8.2.1.6 and 8.2.1.7. Missing data (including data excluded due to subjects discontinuing double-blind study treatment) at each visit will be handled via reference based multiple imputation as described below:

The reference-based multiple imputation assumes that the statistical behavior of the CZP and placebo-treated subjects after discontinuing study medication becomes that of the placebo-treated subjects. Data collected after discontinuation of the double-blind study treatment for both the CZP and placebo groups will be considered missing. Multiple imputations are used to replace missing outcomes for drug- and placebo-treated subjects who discontinued using multiple draws from the posterior predictive distribution estimated from the placebo arm. For binary efficacy variables (ASAS40 at Weeks 12 and 52), imputation will be done on the raw components before assessing the imputed results for ASAS response. For continuous efficacy variables (change from Baseline in BASDAI and BASFI at Weks 12 and 52, change from Baseline in the SI joint SPARCC score at Week 12, change from baseline in ASQoL and Nocturnal Spinal Pain at Week 52), imputation will be done on the raw scores prior to calculating the change from Baseline.

1. For subjects with a non-monotone (intermittent) missing pattern, MCMC will be used to impute their missing intermittent scores including treatment, region and MRI/CRP classification as explanatory variables. This will be done 100 times in order to provide a dataset with monotone missing limiting imputation to in range results.

   After this step there will be 100 datasets containing all subjects however the only missing data will be a monotone missing data pattern. A variable called "_imputation_" will identify each of the 100 imputed datasets output.

2. The remaining missing data for all subjects with a monotone missing data pattern will be imputed using regression using the placebo-treated subjects arm only to impute missing data for both placebo and CZP treatments. The model will contain region, MRI/CRP classification and measurement from previous visit(s) as explanatory variables. This model will be run once for each of the imputed datasets limiting imputation to in range results.

3. For each completed data set, the outcome (response or change from Baseline) will be calculated using the complete datasets (with no missing data).

4. For ASAS40, complete parts 5 and 6 from Section 8.1.3.2 in order to provide odds ratios, 95% CIs and the p-value from the proc mianalyze. For BASDAI, BASFI, SI joint SPARCC, ASQoL and Nocturnal Spinal Pain, complete parts 4 and 5 from Section 8.2.2.2 in order to provide treatment differences, 95% CIs and the p-value from the proc mianalyze.

Additionally, change from Baseline in SI joint SPARCC score at Week 12 is a continuous secondary efficacy variable. The same referenced based multiple imputation procedure specified in this section will be used to account for missing SPARCC data. However, it should be noted that, unlike BASDAI and BASFI, SPARCC score will not be measured at any time points between Baseline and Week 12, meaning that those are the only 2 time points that can be

considered in the evaluation of SPARCC score at Week 12. Comparisons between treatment groups will be made using an analysis of covariance (ANCOVA) model on the imputed data set. The model will include Baseline score, treatment group, region, and MRI/CRP classification.

8.2.3 Supportive and sensitivity analyses of the secondary efficacy variables

Descriptive statistics (number of available observations [n], mean, median, standard deviation, minimum and maximum) will be provided for all secondary efficacy variables. The descriptive analyses will be covered in the tables summarizing the variables over time.

Sensitivity analyses of the secondary binary efficacy variables (ASAS40 at Weeks 12 and 52) as described in Section 8.2 will be as follows:

- Including observed data at Week 52 (or Week 12 as applicable): As described for the primary efficacy variable in Section 8.1.3.1.
- Multiple imputation: As described for the primary efficacy variable in Section 8.1.3.2. Note that as ASAS40 is a composite of 4 different variables, the multiple imputation procedure will be performed on each of these components, and the ASAS40 response will be derived prior to Step 5 based on the multiply imputed datasets.
- Reference-based multiple imputation: As described in Section 8.2.2.2.
- Observed case analysis: As described for the primary efficacy variable in Section 8.1.3.4.

The sensitivity analyses of secondary continuous efficacy variables (the change from Baseline in BASDAI and BASFI at Weeks 12 and 52, the change from Baseline in the SI joint SPARCC score at Week 12, the change from baseline for ASQoL at Week 52 and the change from baseline for Nocturnal Spinal Pain at Week 52) will be as follows:

- Including observed data at Week 52 (or Week 12 as applicable): As described for the primary efficacy variable in Section 8.1.3.1.
- Multiple imputation: As described in Section 8.2.3.1
- Observed case analysis: As described for the primary efficacy variable in Section 8.1.3.4.
- Last Observation Carried Forward (LOCF): If there is missing data at the time point of interest, the last available post-Baseline measurement will be carried forward to that time point (including scheduled or unscheduled visits). This will not apply for the analysis of SI joint SPARCC score at Week 12 since there are no measurements collected between Baseline and Week 12.

8.2.3.1 Multiple imputation of secondary continuous efficacy variables

The continuous BASDAI , BASFI, ASQoL or Nocturnal Spinal Pain scores at each visit will be calculated using the methods described in Section 8.2.1.2, Section 8.2.1.3, 8.2.1.6 and 8.2.1.7. Missing data (including data excluded due to subjects discontinuing double-blind study treatment) at each visit will be handled via multiple imputation as described below:

1. For subjects with a non-monotone (intermittent) missing pattern, MCMC will be used to impute their missing intermittent scores. This will be done 100 times for each subject including treatment arm, region, MRI/CRP classification and limiting imputation to in range results.

After this step there will be 100 datasets containing all subjects however the only missing data will be a monotone missing data pattern. A variable called "_imputation_" will identify each of the 100 imputed datasets.

2. The remaining missing data for all subjects with a monotone missing data pattern will be imputed using regression with treatment arm, region, MRI/CRP classification and measurement from previous visit(s) as explanatory variables. This will be done once for each of the 100 datasets limiting imputation to in range results.
3. The change from Baseline to Week 52 will be calculated using the complete datasets (with no missing data).
4. For each of the 100 imputed datasets (identified by _imputation_ variable), an ANCOVA model, where response is the change from Baseline, with Baseline score as a fixed-effect covariate and treatment group, region, and MRI/CRP classification as fixed-effect categorical factors. The estimand of interest here is the difference in BASDAI/BASFI/ASQoL/Nocturnal Spinal Pain, if all subjects tolerate or adhere to double-blind study treatment. In the context of handling missing data in clinical study settings, this has been referred to as "estimand 3" (Mallinckrodt, 2012).
5. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

8.3 Analysis of other efficacy variables

The efficacy analyses described in this section are not part of the multiplicity-controlled testing procedure described in Section 8. The p-values reported for these analyses will not be adjusted for multiplicity and will be considered nominal. Derivations for these other efficacy variables can be found in Section 8.3.1.

Continuous other efficacy variables will be analyzed using an ANCOVA model including Baseline score as a covariate, and fixed effects for treatment group, region, and MRI/CRP classification. The treatment differences and corresponding 95% CIs will be calculated based upon the adjusted least squares means. Missing values or values observed after discontinuing the double-blind study treatment will be imputed using LOCF. In addition, as described in Section 4.2.3, an observed case analysis will also be performed for subjects still on the original double-blind study treatment. Tables for continuous variables will display descriptive statistics for Baseline, absolute values and change from Baseline at post-Baseline time points.

Categorical other efficacy variables will be analyzed using a logistic regression model with factors of treatment group, region, and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+). If the logistic regression model is unable to converge, then the MRI/CRP classification variable may be dropped from the model to facilitate convergence. Tables for the binary variables will display the responder rates for the various time points. Analyses will be presented in 2 ways (as described in Section 4.2.3). First, they will be presented where the denominator is all subjects in the FAS for the given treatment group. This is essentially a non-responder imputation (NRI) approach as subjects who have not achieved the given outcome (whether observed or not) or subjects who discontinue double-blind study treatment are considered as not having responded. Second, the responder rates will be presented for the FAS using Observed Case data. Subjects still on the original double-blind study treatment and with

response will be analyzed, with the denominator based on the number of observed values at the given time point.

Continuous other efficacy variables to be analyzed using change from Baseline are:

- BASDAI and BASFI at Weeks 1, 2, 4, 8, 16, 20, 24, 28, 32, 36, 40, 44, 48
- ASDAS at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52
- ASQoL at Weeks 1, 2, 4, 12, 24, 36, 48
- Nocturnal spinal pain (NRS) at 1, 2, 4, 8, 16, 20, 24, 28, 32, 36, 40, 44, 48
- Other continuous data from the ASAS components at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52:
  - PGADA
  - Total spinal pain (NRS),
  - Morning stiffness as assessed by the average of BASDAI questions 5 and 6
  - BASMI Lateral Spine Flexion
  - CRP
- BASDAI individual questions 1 (Fatigue), 2 (neck, back or hip pain), 3 (pain/swelling in joints other than neck) and 4 (discomfort) at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52
- BASMI linear score at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52
- Spinal mobility assessments (occiput to wall distance and chest expansion) at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52
- Sacroiliitis grading for structural damage at Week 52 (mean of the right and left grade for all readers). Note: LOCF will not be performed as grading is only measured as Baseline and Week 52
- SI joint SPARCC score at Week 52 and ankylosing spine MRI acuity (ASspiMRI-a) in the Berlin modification at Weeks 12 and 52
- ASAS-NSAID use at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

  Thereby, ASAS-NSAID use at a certain week refers to any intake between this week and the previous week.
- Sleep Problems Index II domains of the MOS Sleep scale at Weeks 4, 12, 24, 36 and 48
- Enthesitis (MASES) at Weeks 1, 2, 4, 8, 12, 16, 24, 32, 40, 48, and 52
- Swollen and tender joint counts at Weeks 4, 12, 24, 36 and 52
- PhGADA at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52
- SF-36, PCS, MCS and individual domains at Weeks 4, 12, 24, 36, 48, and 52
- EQ-5D VAS at Weeks 4, 12, 24, 36, 48, and 52

Categorical other efficacy variables to be analyzed are:

- ASDAS-MI at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32 36, 40, 44, 48,
- ASDAS-CII at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52
- ASDAS ID, MD, HD and vHD at Baseline and Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 (Summary statistics provided only)
- BASDAI50 response at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52
- ASAS40 at Weeks 1, 2, 4, 8, 16, 20, 24, 28, 32, 36, 40, 44, 48
- ASAS20, ASAS5/6 and ASAS partial remission response at Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52
- Sacroiliitis grading for structural damage at Week 52 (change from mNY- negative to mNY-positive)
- SI joint SPARCC score <2 at Weeks 12 and 52
- Uveitis flares, IBD exacerbations and Psoriasis exacerbations at Baseline and Weeks 4, 12, 24, 36, 48 and 52 (Summary statistics provided only)
- EQ-5D 5-Item health status at Weeks 4, 12, 24, 36, 48, and 52

For the 'resource utilization' variables 'number of concomitant medical procedures', 'number of health care provider consultations not foreseen by the protocol', 'number of hospitalizations', and 'number of emergency room visits' descriptive statistics and frequency distributions will be presented for the entire double-blind period.

For the WPS scores, Question 1 responses will be summarized descriptively. Question 2-9 will be summarized by descriptive statistics as well. Treatment comparisons for Question 2 through Question 9 will be performed using a mixed-effect repeated-measures model (MMRM) . For each individual question, a separate MMRM will be fitted for the change from baseline, including fixed effects of baseline, treatment, visit, treatment-by-visit interaction and baseline-by-visit interaction, including a random effect of subject and using an unstructured variance-covariance structure. The Kenward-Rogers method will be applied to estimate the denominator degrees of freedom. If convergence problems arise, the covariance structure will be assumed to be autoregressive first order (AR[1]). If that still leads to numerical problems, the more general case, the Toeplitz (TOEP) covariance structure will be used. If all methods above fail to produce a solution, the covariance structure Compound Symmetry (CS) will be used. The least-square means of the treatment difference by visit including 95% confidence intervals and p-values for the test on treatment differences will be summarized.

8.3.1 Derivation of other efficacy variables

Derivations of other efficacy variables not covered in the primary or secondary variables are provided below.

8.3.1.1 Bath Ankylosing Spondylitis Metrology Index (BASMI)

The BASMI characterizes the spinal mobility of a subject with AS and consists of 5 clinical measures to reflect axial status: cervical rotation; tragus to wall distance; lateral spinal flexion; lumbar flexion (modified Schober); intermalleolar distance. Each of the 5 movements is scored

according the linear BASMI definition (see table below). The mean of the 5 scores provides the BASMI score. The higher the BASMI score the more severe the subject's limitation of movement due to their AxSpA.

BASMI linear definition

S = (21.1 cm –A) / 2.1 cm	For the lateral lumbar spine flexion (mean right/left)
S = (A – 8 cm) / 3 cm	For the tragus-to-wall distance (mean right/left)
S = (7.4 cm – A) /0.7 cm	For the lumbar flexion (modified Schober)
S = (124.5 cm – A) / 10 cm	For the maximal intermalleolar distance
S = (89.3° - A) / 8.5°	For the cervical spine rotation (mean right/left)
Always with the additional condition $0 \leq S \leq 10$	

S = score, A = assessment

For cervical rotation, tragus-to-wall distance and lumbar flexion, take the mean of the left and right measurements, if both are available. Otherwise, the available measurement will be used.

For the lumbar flexion (modified Schober), values greater than 9.0 cm (Maksymowych 2006) will be flagged as invalid and treated as if they were missing values. The below imputation rules apply for BASMI.

If 1 or 2 clinical measures for the BASMI are missing at one visit, the missing measure will be imputed by carrying the last observation forward, and the BASMI will be calculated accordingly. If more than 2 items are missing, the BASMI score will be treated as missing.

8.3.1.2 Total spinal pain

Total spinal pain will be recorded based on a NRS ranging from 0 to 10, where 0 represents no pain and 10 represents most severe pain.

8.3.1.3 SI joint radiographs

SI joint radiographs will be read by two reviewers, with adjudication (if applicable), to assess for the presence and severity of sacroiliitis according to mNY criteria for AS in the right and left SI joint separately.

A grading from 0 to 4 will be assigned corresponding to 0 = Normal, 1 = Suspicious but not definite, 2 = Minimal: some sclerosis, minimal erosion, no marked joint space narrowing, 3 = Moderate: definite sclerosis, both sides of the joint with erosions and/or joint space change, and 4 = Ankylosis: complete obliteration of the SI joint with or without sclerosis. Readers will also classify the subjects as mNY-negative or mNY-positive.

A mean grading will be calculated per subject and visit using the four SI grading results (the left and right joint grades read by the 2 readers). If a third adjudication reading is required, then all 6 grades will be used to calculate the mean grade per visit.

If there is disagreement between the 2 readers in the classification of the subject (mNY-negative or mNY-positive), then the 3rd readers adjudication classification will be used for analysis.

Subjects who are positive at baseline (and hence should not have been enrolled) will be excluded from the categorical endpoint analysis of subjects who change from mNY-negative to mNY-positive during the study.

8.3.1.4 Tender and Swollen Joint Counts (44 joints evaluation)

Tender joint counts (TJC) and swollen joint counts (SJC) will be carried out on the following 44 joints:

- Upper body (4) – bilateral sternoclavicular and acromioclavicular joints
- Upper extremity (26) – bilateral shoulders, elbows, wrists (includes radiocarpal, carpal and carpometacarpal bones considered as a single unit), metacarpophalangeals (MCPs) I, II, III, IV, and V, and thumb interphalangeals (IPs), and proximal IPs (PIPs) II, III, IV, and V
- Lower extremity (14) – bilateral knees, ankles, and metatarsophalangeals (I, II, III, IV, and V)

The assessment for swelling and tenderness is made on 44 joints from the above list. Artificial, ankylosed, and missing joints are excluded from swelling and tenderness assessments.

Each joint is scored for tenderness as follows:

0 = None (not tender)

1 = Positive (tender)

Each joint is scored for swelling as follows:

0 = None

1 = Detectable

TJC and SJC are calculated as the sum of tender and swollen joints, respectively, among the 44 joints. Both TJC and SJC range from 0 to 44.

If there are missing observations for tender or swollen joints then the remaining observations will be assessed and weighted by dividing by number of non-missing and then multiplying by 44 for the joint count. If a joint is not evaluable at Baseline, then that joint is set to missing throughout the study.

If data for more than 50% of the joints are missing at the time of a given assessment, then no imputation will be done and the total TJC or SJC will be set to missing for that visit.

TJC summaries will be based only on those subjects with at least one tender joint at Baseline. Similarly, SJC tables will be based only on those subjects with at least one swollen joint at Baseline.

8.3.1.5 Patient's Global Assessment of Disease Activity (PGADA)

PGADA will be recorded based on an NRS describing how active the subject's spondylitis was on average over the past week. The range of the scale is from 0 to 10, where 0 represents not active and 10 represents very active.

8.3.1.6 Physician's Global Assessment of Disease Activity (PhGADA)

PhGADA is recorded by the physician on a VAS ranging from 0 to 100, where 0 is "very good, asymptomatic and no limitation of normal activities" and 100 is "very poor, very severe symptoms which are intolerable and inability to carry out all normal activities."

8.3.1.7 C-reactive protein (CRP)

For CRP values below the lower limit of quantification (<4mg/L), half the lower limit (2mg/L) will be used as the imputed value.

8.3.1.8 Spinal mobility

The following spinal mobility assessments will be performed in addition to those performed for the BASMI:

- Occiput to wall distance
- Chest expansion

8.3.1.9 Enthesitis (MASES)

The MASES comprises 13 items (bilateral costochondral 1, costochondral 7, anterior superior iliac spine, posterior iliac spine, iliac crest and proximal insertion of the Achilles tendon sites, and the fifth lumbar vertebral body spinous process) (Heuft-Dorenbosch et al, 2003) each scored as 0 = yes or 1 = no and then summed for a possible score of 0 to 13, with higher scores indicating worse enthesitis.

If 7 or more items are available, MASES will be imputed by dividing the sum score with the number of assessments and multiplying the result with 13. If less than 7 times are available, MASES will be treated as missing.

Summaries of MASES will be restricted to the subset of subjects with enthesitis present at Baseline. Presence of enthesitis at Baseline will be defined as a Baseline MASES score >0.

8.3.1.10 Short-Form 36-item Health Survey (SF-36)

The SF-36 (Version 2, standard recall) is a 36 item generic HRQoL instrument that uses a recall period of 4 weeks. Items are grouped into 8 domains as follows: Physical Functioning (10 items), Role Physical (4 items), Bodily Pain (2 items), General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role Emotional (3 items), Mental Health (5 items), and a further unscaled single item (Q2) for perceived stability or change in health (Health Transition) during the last year. The concepts represented by these domains contribute to physical, mental, and social aspects of HRQoL.

The SF-36 domains (subscores) are scored so that a higher score indicates a better health state.

QualityMetric Health Outcomes™ Scoring Software will be used to calculate norm-based scores for the following domains:

- Physical Functioning (PF)
- Role Physical (RP)
- Bodily pain (BP)

- General health (GH)
- Vitality (VT)
- Social Functioning (SF)
- Role Emotional (RE)
- Mental health (MH)
- Mental Component Summary (MCS)
- Physical Component Summary (PCS)

8.3.1.11 ASAS-NSAID score

The ASAS-NSAID score is a tool that has been developed to measure the magnitude of NSAID intake during clinical studies (Dougados et al, 2011). Using the concomitant medication NSAID data, the start and stop dates of each medication will be compared to study intervals to determine the dosage and frequency that each NSAID was being taken during the study. Intervals will be weekly from Week 0 to Week 2, bi-weekly up to Week 4 and then every 4 weeks until Week 52.

Patients not taking NSAIDs in an interval will have an ASAS-NSAID score of 0.

The general formula for calculating the ASAS-NSAID score in an interval is as follows:

- (equivalent NSAID score) × (days of intake during period of interest) × (days per week)/(period of interest in days)

Each of the components of the above calculation are described below:

- Equivalent NSAID score: This is reported in terms of NSAID equivalent dose in mg/day on a 0–100 scale where the 150mg equivalent diclofenac is set to 100. An NSAID equivalence table was developed based on a survey of ASAS members. The table including the consensus equivalence score for various NSAIDs can be found in Appendix 13.3.
- Days of intake during period of interest: Equivalent to the total number of days covered during the period that is being measured.
- Days per week: Proportion of days per week when the NSAID is taken. This is collected in the categories described in the days with intake category listed above. Each category corresponds to a score as follows (score in parentheses):
  - Every day or QD (7/7)
  - ≥5 days/week (6/7)
  - 3-5 days/week (4/7)
  - 1-3 days/week (2/7)
  - <1 day/week (0.5/7)
  - No NSAID intake (0)
- Period of interest in days: Refers to the number of days covered for a given NSAID. If only 1 NSAID was taken during the entire period of interest, this will be the same as days of intake during period of interest.

Dougados, et al provide the following example. If during a period of interest (between two visits) of 6 months, the subject has taken piroxicam 20mg during 4 months and if during this 4-month period he has taken piroxicam 3–5 days per week the calculation is as follows:

- 100 (20mg piroxicam score) × 120 (4 months) × 4/7 (3–5 days/week)/180 (6 months) = 38.1

If the subject has used 10mg piroxicam during the remaining 2 months on 2 days a week, the NSAID score for this period is:

- 50 (10 mg piroxicam score) ×60 (2 months) × 2/7 (1–3 days/week)/180 (6 months) = 4.8

In this example the total score for the 6 month period is 42.9 (38.1 plus 4.8).

For the observed case analysis, only intervals that end on or prior to end of the double-blind treatment period will be included. For the LOCF analysis, all data will be included for all intervals up to Week 52 (1 year) irrespective of whether the subject is on double-blind or open-label study medication.

8.3.1.12 Work Productivity Survey (WPS)

The WPS is a 9 question instrument used to assess the impact of arthritis on productivity within and outside the home during the preceding 4 weeks. [redacted] on a 0 to 10 scale (0=no interference; 10=complete interference). [redacted] on a 0 to 10 scale (0=no interference; 10=complete interference).

In order to make data consistent and amenable to statistical analysis, the following counting rules will be applied to handle out of range and ambiguous answers of the WPS.

These counting rules will be applied prior to conducting any type of statistical analysis of the data.

WPS counting rules

Due to the inter-relation between certain questions of the WPS, the priority order for implementing these specific counting rules is as in the listed order below.

WPS Question 1 (Q1) ([redacted])

- If (Q1=missing) and (Q2>0 or Q3>0 or Q4>0), then Q1=YES.
- If (Q1=missing) and {(Q1.a (1) is not missing) or (Q1.a (2) is not missing)}, then Q1=YES.
- If (Q1=missing) and (Q1.b is not missing), then Q1=NO.

For all rules below, the original value will be kept and displayed in the listings but the corrected value will be considered for the analyses (tables).

- If [redacted]="No" and Job function is not " " then Job function=" ".
- If [redacted]="No" and occupation is not " " then occupation=" ".
- If [redacted]="Yes" and subject's status is not " " then status=" ".

WPS Q2 ([redacted])

- If (Q1=NO), then Q2="." (missing)
- If Q2 =0 or missing (.) and if Q1 ([redacted]) is Missing (.) then Q2=. (replace 0 by ".").

WPS Q3 ([redacted])

- If (Q1=NO), then Q3="." (missing).
- If Q3 =0 or missing (.) and if Q1 ([redacted]) is Missing (.) then Q3=. (replace 0 by ".").

WPS Q4 [redacted]

- If (Q1=NO), then Q4="." (missing).
- If Q4 is out of range, then Q4="." (missing).
- If Q4=0 or missing (.) and if Q1 ([redacted]) is Missing (.) then Q4=. (replace 0 by ".").

WPS Q9 ([redacted])

- If Q9 is out of range, then Q9="." (missing).

WPS Q2 to Q9

For the rule below, the original value will be kept and displayed in the listings but the corrected value will be considered for the analyses (tables).

- If value=X.5 then value=X+1 (for ex: 1.5->2).

With regards to missing observations at Baseline, the following rules apply:

- Q1 (categorical): missing Baseline is not imputed
- Q2-Q9 (discrete): missing Baseline is imputed by the mean of the available subjects, rounded to the closest integer.

For WPS, the following correction rules have to be applied for Q1, Q2, Q3 and Q4 prior to any analysis of the data to make the data consistent and amenable to statistical analysis:

If Q1='No' and Job function is not ' ' then Job function=' '.

If Q1='No' and occupation is not ' ' then occupation=' '.

If Q1='Yes' and subject's status is not ' ' then status=' '.

If Q1='No' and Q2 is not missing, then Q2='.'

If Q1='No' and Q3 is not missing, then Q3='.'

If Q1='No' and Q4 is not missing, then Q4='.'

8.3.1.13 Medical Outcomes Study (MOS) sleep scale

The MOS Sleep Scale is a validated generic self-administered scale measuring specific aspects of sleep. The frequency with which each problem has been experienced during the previous 4 weeks is rated on a 5-point scale ranging from "none of the time" to "all of the time", except sleep quantity, which is reported in hours. All scores are transformed linearly to range from 0 to 100, again with the exception of the sleep quantity subscale, which is scored in hours. Higher scores indicate more of the attribute implied by the scale name (eg, more sleep disturbance, more adequate sleep, or greater sleep quantity).

QualityMetric Health Outcomes™ Scoring Software will be used to calculate the domains of Sleep disturbance, Snoring, Sleep short of breath or headache, Sleep adequacy, Sleep somnolence, Sleep problems Index I, Sleep problems Index II.

8.3.1.14 Health Status (EQ-5D)

The EQ-5D consists of a 5-item health status measure and a VAS. Each of the 5 health states is divided into 3 levels (no problem, some or moderate problems, and extreme problems) and is scored as 1, 2, and 3, respectively. The EQ-5D VAS records the respondent's self-rated health status on a vertical 20cm scale, 0 to 100 graduated (0=worst imaginable health status, 100=best imaginable health status).

The VAS will be evaluated by changes from Baseline and actual scores. The 5 dimensions will be analyzed categorically.

As electronic data capture is being used, ambiguous and out of range answers are not expected. However, if these rules are needed, see Appendix 13.2.

8.3.1.15 Resources Utilization

The following resource utilization data were collected through UCB standardized modules:

- In–patient hospitalization and emergency room visits
- Health care provider consultations not foreseen by the protocol
- Concurrent medical procedures

Summary statistics and frequency distribution (number of subjects by number of medical resources used) will be presented for resource use with onset during the double-blind period for concurrent medical procedures, health care provider consultations, hospital visits and emergency room (ER) visits. ER visits will be extracted from the hospitalizations/emergency room visit eCRF page (if initial entry point emergency room is ticked).

The categories to be displayed for the frequency distributions of the resource use variables will be defined during the DEM meeting based on blinded data review.

A medical resource is allocated only once in its period of onset, as determined by the (start) date of the event. A resource will be attributed in the same way as an AE is considered a treatment-emergent adverse event (TEAE). The same rules for (partially) missing start and end dates as for AEs will be applied for the resource use.

For the same subject only one hospitalization will be considered if "start date of the second hospitalization - end date of the first hospitalization ≤ 1". For missing end dates of hospitalizations (missing discharge dates) the following rules will be applied:

If there is a subsequent hospitalization:

- If the initial entry point and relationship are the same between the two hospitalizations, then the first hospitalization will be grouped with the next one and counted as one hospitalization. In this case the length of the hospitalization will be computed as follows:
  - If the discharge date of the 2nd hospitalization is non-missing, then length of stay =2nd hospitalization discharge date – 1st hospitalization admission date +1;
  - Else, length of stay = last non missing visit date – 1st hospitalization admission date + 1
- Otherwise, if either the entry point or the relationship of the two hospitalizations is different, then both hospitalizations will be counted as distinct. In this case the length of the 1st hospitalization will be computed as follows:
  - Length of stay = (2nd hospitalization admission date -1) – 1st hospitalization admission date + 1 (ie, 2nd hospitalization admission date – 1st hospitalization admission date)

In case there is no subsequent hospitalization, then the length of the hospitalization is calculated as length of stay = last non missing visit date – hospitalization admission date + 1

In case of complete consultation date, count only once for a same subject, same consultation date, same location and same provider.

If the procedure name, start date and relationship are the same, then only one procedure is counted, otherwise if at least one variable among procedure name, start date or relationship is different, distinct/several procedures are counted.

If concomitant medical procedures, health care provider consultations not foreseen by the protocol, and hospitalizations/emergency room visits are not available during the study, the respective number variable will be set to 0.

8.3.1.16 Extra-articular assessments

The evolution of associated nonmusculoskeletal features including inflammatory bowel disease, psoriasis, uveitis (including their severity), and flare rate history will be assessed.

9 PHARMACOKINETICS , PHARMACODYNAMICS, AND PHARMACOGENOMICS

9.1 Pharmacokinetics

Certolizumab pegol plasma concentration data will be summarized by treatment group overall, and by Anti-CZP antibody (ADAb) status of individual subjects (as defined below), for each scheduled visit at which samples were taken, for the SS. Samples collected out of window may be excluded from the analysis. All CZP concentrations will be reviewed after unblinding by study statistician and clinical pharmacologist to ensure all values are plausible, and values deemed anomalous will be excluded from summary statistics. For concentration data collected in the open-label period, subjects randomized to placebo will only have their OL-CZP data on or after Week 12 open-label visit presented, to ensure the subject is at steady state. For subjects

randomized to CZP, their double-blind and OL-CZP data will be presented at all available visits. Geometric mean, geometric coefficient of variation (CV), 95% CIs, arithmetic mean, arithmetic SD, median, minimum, and maximum, will be presented. Geometric mean CZP plasma concentration time curves will be plotted by treatment group, and by antibody status for subjects receiving CZP.

The value of blood sample measurements that are deemed to be below the level of quantification (BLQ), will be set to half the lower level of quantification (LLOQ) for analysis purposes. The summary statistics will only be displayed if at least two-thirds of the values are above the LLOQ.

Individual subject plasma concentrations for CZP, anti-CZP antibody (ADAb) titres, ASDAS scores and dose levels versus time will be produced on the same graph. Two Y-axes on the left will represent the CZP concentrations and anti-CZP levels. The Y-axis on the right will show the ASDAS score. The x-axis will represent time (weeks) with lines showing the treatment and dose.

9.2 Pharmacodynamics

Not applicable.

9.3 Pharmacogenomics, biomarkers and cytokines

Pharmacogenomics, biomarkers and cytokine data analysis will be described in a separate analysis plan and report.

10 IMMUNOGENICITY

10.1 Available data

Anti-CZP antibodies (ADAb) will be measured and summarized at Baseline, Weeks 1, 2, 4, 12, 24, 36, 52/WD, and the Follow-up visit (if applicable). In addition, the ADAb will be assessed in subjects who withdraw from study drug and transition to OL-CZP.

A cut point will be determined by the bioanalytical laboratory during assay validation. This cutpoint will be used to determine the status of ADAb in the test sample as above the cut point (ACP) or below the cut point (BCP). For any ADAb test samples with results that are ACP, a further confirmatory assay will be performed, the results of which will be determined as either ‘confirmed positive’ (CP) or ‘not confirmed positive’ (NCP).

The following definitions will be applied regarding classification of test samples:

- An ADAb status will be confirmed as positive for any sample with an ADAb level that is ACP and CP
- An ADAb status of negative will be concluded for any sample with an ADAb level that is either BCP or ACP and NCP

Confirmed positive samples will be titrated. The dilution factor will be reported. The titer represents the last dilution factor of the sample’s titration series still scoring positive in the screening ADAb assay.

In a subset of samples, the ADAb response will be characterized for their neutralizing potential. The subset will be selected according to which samples have drug levels to allow testing, and will cover baseline, the visit with the highest titre of ADAb on treatment, and follow up.

Selection methods will be specified in the bioanalytical plan. A cut point will be determined by the bioanalytical laboratory. This cutpoint will be used to determine the status of neutralizing ADAb in the test sample as below the cutpoint (nADA positive) or above the cutpoint (nADA negative).

10.2 Subject classification

Subjects will receive an overall classification, inclusive of Baseline and Post-Baseline results, and be classified as follows based on the ADAb assay results:

- ADAb negative: no confirmed positive ADAb samples at any of the sampling time points
- ADAb positive: confirmed positive ADAb samples at one or more sampling time points
- Missing: relevant samples are missing

Subjects baseline classification will be based on the ADAb assay test results at baseline

- Pre-ADAb negative: negative ADAb baseline sample
- Pre-ADAb positive: confirmed positive ADAb baseline sample
- Missing: no baseline ADAb sample

Baseline is defined as the sample immediately prior to or on the same day as first treatment with CZP. For subjects randomized to CZP, baseline will be Week 0 of the randomized treatment period and for subjects who were randomized to placebo but then received OL-CZP, baseline will be Week 0 of escape OL-CZP.

Subjects will receive a treatment-emergent classification based on the combination of the post-baseline ADAb assay results as well as the baseline ADAb sample result

- Treatment emergent ADAb negative: (i) subjects with no confirmed positive ADAb samples at any of the sampling time points, (ii) pre-ADAb positive subjects with all post baseline samples either ADAb negative or confirmed positive ADAb but with a titre below a pre-defined fold increase from the Baseline value (the fold increase from Baseline required to meet these criteria will be defined with the development of the assay and will be included in the TFLs)
- Treatment emergent ADAb positive: (i) pre-ADAb negative subjects with one or more confirmed positive samples post baseline, (ii) pre-ADAb positive subjects with one or more confirmed positive ADAb sample post baseline with a titre above a pre-defined fold increase from the Baseline value (the fold increase from Baseline required to meet these criteria will be the same as that defined for treatment emergent ADAb negative and will be included in the TFLs)
- Missing: relevant samples are missing

In addition to the ADAb classifications, subjects will also receive an overall nADA classification, inclusive of baseline and post-baseline results, on the nADA assay results

- nADA negative: no nADA positive samples at baseline or post-baseline
- nADA positive: one or more positive samples at baseline or post-baseline
- Missing: relevant nADA samples are missing, e.g. if subject had samples selected for nADA testing based on their ADAb levels, but there was insufficient sample left for nADA testing.
- Not Applicable (NA): If a subject was ADAb negative (i.e. had no positive ADAb samples)

10.3 Analysis

Immunogenicity will be assessed through summary tables and figures, and listing of individual results by subject.

All analyses will be run on the safety population, unless specified otherwise. ADAb and nADA data will be reviewed after unblinding to ensure all values are plausible, and values deemed anomalous will be excluded from summary statistics.

The number and percentage of each subject in the above classifications (ADAb and nADA) will be reported. The prevalence of immunogenicity will be reported per time point, defined as (cumulative) proportion of subjects having confirmed positive ADAb samples at any point up to and including that time point. Missing samples will not be included in the denominator.

Time to achieving treatment-emergent ADAb positivity will be analyzed based on Kaplan-Meier approach, subjects will be considered to have an event at time where treatment emergent ADAb positive is first achieved. Subjects classified as treatment-emergent ADAb negative will be censored at time of last available ADAb result. Discontinued subjects prior to Week 52 will be censored at the last ADAb result prior to discontinuation if they have not become ADAb Positive. Subjects will be summarized based on completing 52 weeks of treatment, discontinuing prior to Week 52, PBO->OL CZP and CZP->OL CZP treatment groups.

Immunogenicity data will be correlated with PK and efficacy endpoints. No formal inferential statistics (p-values) will be derived. The following types of outputs will be produced:

- Summary of ASDAS-MI responders at Week 12 and 52 as a function of ADAb titer. This will be repeated for ASAS40 responders at Week 12 and 52. This will also be presented graphically.
- Spaghetti plots of ADAb titre (Y-axis) against time (X-axis) for treatment emergent ADAb positive subjects and treatment emergent ADAb negative subjects separately for CZP and Placebo (i.e. 4 plots). The CZP plots will have different line patterns for W52 completers and W52 discontinuers.
- Box plots of all (valid) CZP concentrations (Y-axis) versus ADAb titer (X-axis), Y-axis presented in linear and logarithmic scale.

Immunogenicity will also be correlated with possible safety findings.

A summary table of all TEAEs (by SOC, HLT and PT) by TE ADAb Status. For this summary, subjects will be categorized using the treatment-emergent ADAb classification, and will be presented for TEAEs occurring prior to becoming treatment emergent ADAb positive, TEAEs occurring after becoming TE ADAb positive, and TEAEs for subjects who remained TE ADAb negative. This summary may be produced using a titer threshold (to be determined from the data) instead of or in addition to TE ADAb Status.

11 SAFETY ANALYSES

The SS will be utilized for safety analyses.

11.1 Extent of exposure

There are 4 different concepts for calculating exposure during the double-blind treatment period.

1. This approach will look at the number of doses received, which is defined as dosing days. Days with 2 injections (i.e. at Week 0, 2 and 4) are counted as 1 dosing day if either injection is given).

2. For the CZP 200mg and placebo treatment arms, duration of exposure to study medication will be calculated as:

Date of last administration of double-blind CZP 200mg or placebo study medication – date of first administration of CZP 200mg or placebo study medication + 14 days (14 days are included in this definition as this is the dosing interval for maintenance of subjects).

If a subject dies during the exposure period (first injection to last injection + 14 days), the exposure period will end with the death date.

For subjects discontinuing from the study before Week 52, the 2-week period after last double-blind injection will be utilized.

3. For the study exposure of a subject, 5 half-lives of CZP will be taken into account. Hence, a subject will be regarded as being exposed to study drug from first double-blind injection to last double-blind injection + 70 days. The days of drug holidays beyond 70 days will be subtracted.

If a subject dies during the exposure period (1st injection to last injection + 70 days), the exposure period will end with the death date.

For subjects discontinuing from the study before Week 52, the 70 day period after last injection will be utilized.

4. This approach will be the nearly identical to approach 2. However, exposure will be censored at the first occurrence of the AE to be considered for analysis (a separate calculation has to be performed for each preferred term). The different exposure duration for the respective AEs will only be displayed in the AE tables for exposure-adjusted incidences and will not be summarized in the exposure table.

Exposure to the OL-CZP treatment will also be calculated using the above 4 methods considering only dosing during the time the subject is receiving OL-CZP study medication prior to Start of SFE. Exposure during the SFE period will be calculated using methods 2, 3 and 4 assuming first dose in the SFE period starts when the subject takes their loading dose/first dose of OL-CZP in the SFE period and ends when the subject has their last administration of study medication (or if missing, the date of withdrawal from the SFE). Total CZP incl DB and OL

exposure will be calculated using all 4 methods, by summing the exposure to CZP during the double-blind and OL- CZP periods. Total CZP incl DB, OL, and SFE OL will be calculated using methods 2, 3 and 4, by summing the exposure to CZP during the double-blind, OL-CZP and SFE periods. Note that for Total CZP incl DB, OL, and SFE OL method 1 will not be calculated as the SFE period does not collect data on dose administration. Exposure to OL-OT will not be calculated.

For the first 3 approaches, tables will summarize exposure for the placebo, CZP 200mg Q2W, OL-CZP treatment groups (split by the treatment taken during the double-blind period), SFE OL-CZP,Total CZP incl DB and OL and Total CZP incl DB, OL, and SFE OL (for methods 2 and 3 only).

11.2 Adverse events

AE start dates will be examined to determine if they are treatment-emergent and attributable to the double-blind period, open-label period or SFE period. AEs occurring either before double-blind study drug administration (pre-treatment) or outside of the windows described below will be defined as non-treatment emergent.

Table 11–1: Assignment of Adverse Events to Study Periods

Type of Subject	Assignment Rule Based on AE Start Date	Assignment
Subjects who do not enter the open-label period and do not enter SFE period	Start date is on or after first study drug administration during the double-blind period and on or before the last study drug administration in the double-blind period + 70 days.	Double-blind TEAE
Subjects who do not enter the open-label period but do enter SFE period	Start date is on or after first study drug administration during the double-blind period and on or before the last study drug administration in the double-blind period + 70 days and prior to loading dose/first dose administration in SFE period	Double-blind TEAE

Table 11–1: Assignment of Adverse Events to Study Periods

Type of Subject	Assignment Rule Based on AE Start Date	Assignment
Subjects who enter the open-label period	1. Start date is on or after first study drug administration during the double-blind period and on or before the last study drug administration in the double-blind period + 70 days and before the start date and time of OL-CZP or OL-OT. **Note:** If a subjects continues in the study with OL-OT visits but without taking any relevant other medication, there will be no start date of the other treatment period and all AEs with a start date within 70 days after last administration will be assigned to the DB period.	Double-blind TEAE
	2. Start date is on or after the start date of OL-CZP and on or before the last study drug administration in the OL-CZP period + 70 days and • before the start date of OL-OT (for subjects moving into OL-OT), or • before the first dose administration in SFE period (for subjects moving into SFE period) •	Open-label CZP TEAE
	3. Start date is on or after the start date of OL-OT. **Note:** Other treatment adverse events will not be summarized, but only presented in listings	Open-label other treatment TEAE
Subjects who enter the open-label SFE period	Start date is on or after the loading dose/first dose administration in SFE period and on or before the last study drug administration in the SFE period + 70 days.	SFE TEAE

If AE intensity or relationship is missing, then the given event will be imputed as severe or related, respectively.

The frequency of all AEs including TEAEs will be presented for each treatment group separately by System Organ Class, high level term, and preferred term. The data will be displayed as number of subjects experiencing the AEs, percentage of subjects, and number of AEs. Certain summaries will also include exposure-adjusted incidence rates and event rates. TEAEs will be summarized by treatment and period as described in Section 3.6.

The following AE summaries will be presented:

- Overview of TEAE

- TEAE
- Serious TEAE
- Non-serious TEAE
- TEAE with fatal outcome
- TEAE leading to permanent withdrawal of study medication
- Severe TEAE (included in TEAE table by intensity)
- Drug-related TEAE (included in TEAE table by relationship)
- Serious TEAE by relationship
- Non-serious TEAE by relationship
- Fatal TEAE by relationship
- TEAE of special interest (see below)
- TEAE sorted by incidence of PTs in the CZP 200mg group (SOC and higher level term [HLT] will not be utilized)
- Non-serious TEAE with an incidence of more than 5% in 1 of the 2 randomized groups (HLT will not be utilized)
- Non-serious TEAE with an incidence of more than 5% in 1 of the 2 randomized groups by relationship (HLT will not be utilized)
- TEAE subject numbers
- TEAEs with a CZP incidence ≥ 1% and CZP incidence > PBO incidence

The AEs of interest and the approach for summarizing them is briefly described below. Further information is provided in the guidance document (AEs of Interest – Cimzia Program 2018-01-05).

1. Serious infections, including opportunistic infections. Serious infections will be summarized using the Serious TEAE table. No separate table is planned. In addition, opportunistic infections (including tuberculosis) will be presented in a table using UCB-defined search criteria.
2. Malignancies, including lymphoma. These will be presented in 2 tables using the Standardized MedDRA Query (SMQ) criteria "Malignant or unspecified tumours" and "Malignant tumours" respectively.
3. Serious cardiovascular events (also called major adverse cardiac events or MACE). These will be presented in a table including all serious TEAEs with the SMQs of "Haemorrhagic central nervous system vascular conditions", "Conditions associated with central nervous system haemorrhages and cerebrovascular accidents", and "Ischaemic central nervous system vascular conditions" with the exception of events coding to a PT of "Transient ischaemic attack", including all serious TEAEs with the HLT of "Ischaemic coronary artery disorders" except events coding to PTs of "Chest Pain" or "Chest discomfort" and including all serious

TEAEs with HLTs of "Heart Failures NEC", "Left Ventricular Failures", or "Right Ventricular Failures" and which also code to the SOC of "Cardiac Disorders".

4. Congestive heart failure. These will be manually identified by the study physician from the TEAE table. No separate table is planned.
5. Demyelinating-like disorders will be presented in table which is based on the SMQ = "Demyelination". The SMQ search should include all TEAEs which code to a PT included in Scope=Narrow group within the SMQ. TEAEs which code to a PT included in the Scope=Broad group within the SMQ should be excluded from the search.
6. Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia. These will be presented in a table using the criteria SMQ = "Haematopoietic cytopenias" in the subset of Serious TEAEs.
7. Serious bleeding events. These will be presented in a table using the criteria SMQ = "Haemorrhage terms (excl laboratory terms)" in the subset of Serious TEAEs.
8. Lupus and lupus-like illness. These will be manually identified by the study physician from the TEAE table. No separate table is planned.
9. Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, anderythema multiforme). These will be manually identified by the study physician from Serious TEAE table. No separate table is planned.

The tables for 1, 2, 3, 5, and 6 above, will include the exposure-adjusted incidence rate (EAIR) with associated 95% CI, and the exposure-adjusted event rate (EAER) as described below.

Although not officially AEs of interest, the following events will also be summarized as described in the AEs of Interest – Cimzia Program 2018-01-05 guidance document.

1. Hepatic events. These will consist of a subset of all TEAEs, identified using the following 5 SMQs: Cholestasis and jaundice of hepatic origin; Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions; Hepatitis, noninfectious; Liver-related investigations, signs and symptoms; and Liver-related coagulation and bleeding disturbances.
2. Hypersensitivity reactions and anaphylactic reactions. Hypersensitivity reactions will be summarized as any TEAEs occurring on the same day or the day after injection was received, which code to the following preferred terms: Administration site hypersensitivity, Documented hypersensitivity to administered product, Drug hypersensitivity, Hypersensitivity, Hypersensitivity vasculitis, Infusion site hypersensitivity, Injection site hypersensitivity, Medical device site, hypersensitivity, Type II hypersensitivity or Type IV hypersensitivity reaction. Anaphylactic reactions will be defined using an algorithmic approach as described in the "AEs of Interest – Cimzia Program 2018-01-05" guidance document.

Because subjects will be able to adjust background medications during the study, some additional AE tables may be prepared in which events occurring while on certain background medications will be summarized. The list of these supportive tables is expected to be as follows but other subsets of TEAEs may be explored:

- TEAEs reported after starting a new biologic, but within 10 weeks of stopping CZP

- TEAEs reported one month after changing NSAID type
- TEAEs reported three months after changing or adding a DMARD
- TEAEs reported within one month of an addition of oral corticosteroids or 50% increase in dose

The purpose of these tables will be to assess whether any observed treatment differences in the AE profile may be due, in part, to these prespecified background medications.

A TEAE table will also be presented for the 'anti-CZP antibody status' subgroup defined in Section 10 . Only subjects exposed to CZP and only TEAEs occurring after first dose of CZP will be considered. A further column will be presented summarizing TEAEs occurring after the onset of the positive antibody status. The EAIR will be presented in addition to the associated 95% CI, and the EAER.

The TEAE incidence rates will also be adjusted for exposure (as calculated using methods 3 and 4 in Section 11.1) and reported by 100 subject years of exposure. 100 subject-years is defined as the sum of the exposure / number of subjects *100. Two approaches will be applied to adjust for exposure. One will only use the first occurrence of an AE with corresponding exposure (EAIR) and the second approach will use all AEs and the entire exposure (EAER).

For the EAIR, the first occurrence of an TEAEs for a certain treatment group will be utilized (either placebo or CZP 200mg Q2W for the double-blind period or OL-CZP) and divided by the sum of exposure of all subjects in the respective treatment group, where subjects experiencing the respective AE will be censored at the time of occurrence of the AE. The EAIR will be multiplied by a factor of 100 to give a rate per 100 subject-years.

For the EAER, all TEAEs for a certain treatment group will be utilized (either placebo or CZP 200mg Q2W for the double-blind period or OL-CZP) and divided by the sum of exposure of all subjects in the respective treatment group. The EAER will be multiplied by a factor of 100 to give a rate per 100 subject-years.

The summary of TEAEs, serious TEAEs, and TEAEs leading to permanent withdrawal of study medication will include the EAIR (with corresponding 95% exact CI) and EAER. The confidence interval for the EAIR will be based on Poisson rate CIs. The bounds of the exact 95% CIs are estimated by

$$\text{lower bound} = \frac{1}{2 \cdot t} \cdot \chi^2_{2 \cdot \text{number of patients with events}, 0.025} \quad \text{and} \quad \text{upper bound} = \frac{1}{2 \cdot t} \cdot \chi^2_{2 \cdot (\text{number of patients with events}+1), 0.975}$$

$\chi^2_{n,\gamma}$ denotes the chi²-distribution with n degrees of freedom and quantile γ and t is the exposure censored at the time of occurrence of the AE.

Date imputation for incomplete or missing start and/or stop dates

Where an AE start date is (partially) missing, the AE will be considered TE if possible.

Imputation rules provided in Section 4.2.4 are based on the assumption that if the start date is incomplete, either day only is missing, or day and months are missing, or date is completely missing.

Although the algorithms for treatment-emergence depend on the onset date, imputation rules are provided for resolution date as well, as these may be needed for certain statistical analyses, such as an analyses of AE prevalence or AE duration.

In order to identify differences between CZP and placebo with respect to TEAEs, the relative risk (CZP/placebo) of the most common TEAEs (incidence >1% for the PT in the CZP treatment group) will be presented graphically by descending relative risk including the 95% CI.

Listings for TEAEs, serious TEAEs, TEAEs leading to withdrawal of study medication, and TEAEs with fatal outcome will be provided. A glossary for the reported terms will also be generated utilizing SOC, HLT, and PT.

11.3 Clinical laboratory evaluations

The changes from Baseline in laboratory evaluations will be analyzed over time for the SS. In addition, last value (end of treatment), minimum value during treatment, and maximum value during treatment will be analyzed by period (double-blind and OL-CZP). End of treatment will be defined as last visit not including the Follow-up visit. During treatment for the minimum and maximum calculation will also exclude the Follow-up visit.

Shift tables concerning the normal range at end of treatment, minimum and maximum shift at any time will also be produced for each hematology and biochemistry laboratory parameter. The shifts will be categorized using L, N, H, missing, and total.

The number and percent of subjects with markedly abnormal (≥grade 3 by RCTC) hematology or biochemistry values will be summarized at Any Visit, On Treatment (excluding the Follow-up visit) and by visit separately by period (double-blind or OL-CZP). Subject numbers for subjects with any markedly abnormal hematology or biochemistry value will be tabulated. Values fulfilling the criteria below will be classified as marked abnormal high (MH) or marked abnormal low (ML). If no lower (upper) limit is given, the classification ML (MH) is not applicable.

- Hemoglobin < LLN and decrease from Baseline >2g/dL
- Hemoglobin <8g/dL
- White blood cells <2000/µL
- Lymphocyte count <1000/µL
- Neutrophil count <1000/µL
- Platelet count <50000/µL
- ALT >3x upper limit normal (ULN)
- AST >3x ULN
- ALP >3x ULN
- Bilirubin ≥2x ULN
- Creatinine >1.8x ULN
- Calcium >12.5mg/dL

- Calcium <7mg/dL
- CK >4x ULN
- Glucose >250mg/dL
- Glucose <40mg/dL
- Potassium >6.4mmol/L
- Potassium <3mmol/L
- Sodium <125mmol/L
- Uric acid ≥3x ULN

The liver function test elevations will be displayed in an incidence table for the entire double-blind treatment period (including the Follow-up visit) and separately for the OL-CZP treatment period. A shift table will also be presented for double-blind and OL-CZP periods separately showing the change from baseline to maximum post-baseline category (<=1xULN, >1-<2xULN, 2-<3xULN and >=3xULN).

If a repeat sample is taken, the repeated sample data will be used when possible. If the value of a parameter collected at the scheduled visit is missing and an additional sample associated with this visit is taken before the next scheduled visit, the missing value will be replaced by this value. Early Withdrawal Visits will be assigned to what would have been the next scheduled visit.

In the Urinalysis, microscopy (WBC, RBC, casts, crystals, and bacteria) will be performed only when there are abnormalities on the dipstick. This data will be listed and not presented in tables.

11.4 Vital signs, physical findings, and other observations related to safety

11.4.1 Vital signs

The changes from Baseline in vital signs will be analyzed over time for the SS. In addition, the last value (end of treatment), minimum value during treatment, and maximum value during treatment will be analyzed by period (double-blind and OL-CZP). End of treatment will be defined as last visit not including the Follow-up visit. During treatment for the minimum and maximum calculation will also exclude the Follow-up visit.

Early Withdrawal Visits will be assigned to what would have been the next scheduled visit.

The number and percent of subjects with abnormal vital sign values will be summarized by visit and for any visit. Abnormal vital sign results are defined as follows.

Table 11–2: Definition of Abnormal Vital Signs

Vital Sign Parameter	Abnormally Low	Abnormally High
Systolic Blood Pressure (mmHg)	<= 90 and decrease of >=20	>=180 and increase of >=20
Diastolic Blood Pressure (mmHg)	<=50 and decrease of >=15	>=105 and increase of >=15
Pulse Rate (bpm)	<=50 and decrease of >=15	>=120 and increase of >=15

11.4.2 Electrocardiograms

Not applicable.

11.4.3 Other safety variables

11.4.3.1 Weight

The changes from Baseline in weight will be analyzed over time in the SS.

11.4.3.2 Pregnancy testing

Pregnancy testing will consist of serum testing at Screening and Follow-up and urine testing (dipstick) at Baseline, Week 0 of the alternative study assessment for subjects administering either OL-CZP or OL-OT) and at Week 52/WD. No tables will be generated and data will be listed only.

11.4.3.3 Physical assessments

Physical examination will be performed at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 24, 36, 52/WD and at the Follow-up visit (8 weeks after the Week 52/WD visit for subjects not participating in the SFE period). Physical examination findings will be recorded in the eCRF only at Screening. Physical examination data will be listed only.

11.4.3.4 Tuberculosis assessments

The TB assessments at Screening will only be performed to verify the eligibility criteria (presence of active TB or new latent TB infection). These data will be presented as Baseline characteristics (see Section 6.2).

The TB assessments during the study will be utilized to check if a subject has to be withdrawn from the study. QuantiFERON-TB Gold Tuberculosis Test Results will be presented by Visit including End of Treatment.

12 REFERENCES

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13 APPENDICES

13.1 Handling of questionnaire data

The following rules will apply for analysis of (1) out of range and (2) ambiguous answers (ie, invalid or unable to interpret answers) to questionnaires completed by subjects:

In case of out of range answer (ie, an answer that does not correspond to any possible response proposed in the questionnaire, eg, "?", "I don't know," or any value superior or inferior to the ones specified in the response options): the answer will be scored "missing".

However, in case the subject selected one of the proposed responses but added a comment (for instance "6 +++" or "5 ?"), the response (ie, "6" or "5") will be retained for scoring but not the comment (ie, "+++" or "?").

In the same way, if the subject selected one of the proposed responses but added a value superior or inferior to the ones specified in the responses options (for instance, "4/5" or "-1/2" on a 5-point scale ranging from 0 to 4), the response corresponding to the possible responses options (ie, "4" or "2") will be retained for scoring but not the values superior or inferior to the responses options (ie, "5" or "-1").

In case of ambiguous answer (ie, multiple responses to a question allowing only a single response, a response marked between two allowed responses):

Multiple responses to a question allowing only a single response:

- If half or more responses are marked (ie, 4 responses marked on a seven point scale, 3 responses marked on a 5-point scale, 2 responses to a Yes/No item…): the answer will be scored "missing".
- If less than half responses are marked:
  - if the responses are NOT adjacent to each other: the answer will be scored "missing",
  - if the responses are adjacent to each other ("2/3" or "2/3/4", for instance), the more severe score will be retained.

If a response is marked between two allowed responses (for instance, the subject marked his/her response between 2 and 3 on a 4-point scale allowing only responses 1, 2, 3 and 4): the nearest more severe score will be retained.

If a response expected to be stable over time (eg, education) is varying over time no corrective action is foreseen and data will be utilized as reported.

If the EQ-5D VAS contains 2 answers, the most severe answer will be retained.

Please see Section 8.3.1.12 for special rules applicable to the WPS.

13.2 ASAS-NSAID equivalent score

Table 13–1: ASAS-NSAID equivalent score

NSAID	Consensus dose comparable to 150mg of diclofenac (in mg)
Dicloflenac	-
Naproxen	1000
Aceclofenac	200
Celecoxib	400
Etodolac	600
Etoricoxib	90
Flurbiprofen	200
Ibuprofen	2400
Indometacin	150
Ketoprofen	200
Meloxicam	15
Nimesulide	200
Phenylbutazone	400
Piroxicam	20
Tenoxicam	20

14 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN (SAP)

14.1 AMENDMENT 1

Rationale for the amendment

The analysis plan was updated to ensure consistency with the substantial protocol amendment 1, which included several changes to clarify and /or add supporting information regarding the procedures and assessments, and to remove inconsistencies and errors. A range of sensitivity analyses were added into the protocol after discussion with the regulatory authorities, to evaluate the impact of missing data on the analysis of the primary efficacy variable.

As the original SAP was finalized to aid regulatory discussion and the subsequent changes were substantial, it was considered not necessary to document in detail all modifications and changes in this section. However, a brief summary of changes are provided below:

- Protocol scheduled assessments updated for consistency with protocol amendment 1
- Safety Set definition updated to match protocol amendment 1
- The use of graphs for individual plasma concentrations for CZP and anti-CZP levels versus time for consistency with protocol amendment 1
- Methods for handling missing data and sensitivity analyses of efficacy endpoints updated for consistency with protocol amendment 1
- Further detail provided on the analysis of data after a subject discontinues from the double-blind period
- Imputation of partial dates rules updated
- Further detail provided on subgroup analyses
- Other changes made in this amendment are to provide clarification or are administrative in nature, including minor editorial changes to abbreviations

14.2 AMENDMENT 2

Rationale for the amendment

The analysis plan was updated to ensure consistency with protocol amendment 3, which included an additional SFE period, for an additional 2 years, where subjects may receive open-label CZP treatment. All modifications are detailed below.

Change #1

AS0006 has been replaced with AS0006 (C-AXPAND) on the title page and sections 1, 2 and 2.3.

Change #2

DEM, SMQ and SFE were included as acronyms. IVRS was corrected to be IXRS throughout.

Change #3

Section 2:

AS0006 is a randomized, double-blind, parallel-group, placebo-controlled study, consisting of 52 weeks of treatment with certolizumab pegol (CZP) and a follow-up period for 8 weeks after Week 52/Withdrawal [WD] visit which is 10 weeks after the last administration of study medication.

Was changed to:

The C-axSpAnd study (AS0006) is a randomized, double-blind, parallel-group, placebo-controlled study, consisting of 52 weeks of treatment with certolizumab pegol (CZP), followed by a follow-up period for 8 weeks after the Week 52/Withdrawal [WD] visit which is 10 weeks after the last administration of study medication or a 2 year extension with open-label CZP treatment.

Change #4

Section 2.2.3:

Anti-CZP antibody (ADAb) concentrations will be measured and summarized at Baseline, Weeks 1, 2, 4, 12, 24, 36, 52/WD, and the FU visit. In addition, the anti-CZP Ab concentrations will be assessed in subjects who withdraw from study drug and transition to open-label CZP. The number and percentage of subjects with anti-CZP antibody concentrations above 2.4 units/mL will be reported as follows:

- Number and percentage of subjects with ADAb > 2.4 units/mL at the time of each visit
- Number and percentage of subjects with ADAb > 2.4 units/mL at any visit during treatment (not including post treatment withdrawal or Follow-up visit)
- Number and percentage of subjects with ADAb > 2.4 units/mL at any visit including post treatment withdrawal or Follow-up visit

Was changed to:

Anti-CZP antibody (ADAb) concentrations will be measured and summarized at Baseline, Weeks 1, 2, 4, 12, 24, 36, 52/WD, and the Follow-up visit (if applicable). In addition, the anti-CZP Ab concentrations will be assessed in subjects who withdraw from study drug and transition to open-label CZP. The number and percentage of subjects with anti-CZP antibody concentrations above a defined cut point will be reported as follows:

- Number and percentage of subjects with ADAb > defined cut point at the time of each visit
- Number and percentage of subjects with ADAb > defined cut point at any visit during treatment (not including post treatment withdrawal or Follow-up visit)
- Number and percentage of subjects with ADAb > defined cut point at any visit including post treatment withdrawal or Follow-up visit

The cut point to use will be agreed after the sample analysis at the data evaluation meeting (DEM) prior to database lock and unblinding.

Change #5

The following text added as the last sentence in section 2.3 "At the completion of the Week 52 visit assessments, eligible subjects may receive open-label CZP treatment for an additional 2 years in an open-label, Safety Follow-up Extension (SFE) period."

Change #6

Section 2.3.1:

Period 2 (Double-blind period) – Week 0 to Week 52, placebo-controlled.

Eligible subjects will be allocated to the following double-blind study treatments in a 1:1 ratio:

- CZP administered sc at the loading dose of CZP 400mg Q2W at Weeks 0, 2 and 4 followed by CZP 200mg Q2W (starting at Week 6)
- Placebo

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments (including placebo) will be administered sc at the study site. At the Week 0, 2, 4, 6, and 8 visits, the administration must be done by dedicated, unblinded, and adequately trained site personnel. At the Week 10 and 12 visits, the subject will receive training on self-injection and the study treatment will be self-administered under the supervision of the unblinded study personnel. At Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50, the study treatment administration should preferably be done by the unblinded study personnel, or alternatively by self-injection of the subject under the supervision of the unblinded study personnel.

Period 3 (Follow-up period):

All subjects, including those withdrawn from the double-blind study treatment, will have a Follow-up visit, 8 weeks after Week 52/WD visit (10 weeks after their last administration of study medication).

Subjects who discontinue the double-blind study treatment and enter open-label treatment with CZP will be assessed 2 and 4 weeks after open-label CZP treatment has been initiated and every 12 weeks thereafter. Alternatively, subjects who discontinue the double-blind study treatment and receive other treatment (including biologics) will be assessed every 12 weeks after initiation of the other treatment.

The schedule of study assessments is provided in Section 5.2 of the protocol.

A schematic diagram of the study design is provided in Section 5.3 of the protocol.

Has been changed to:

Period 2 (Double-blind period) – Week 0 to Week 52, placebo-controlled.

Eligible subjects will be allocated to the following double-blind study treatments in a 1:1 ratio:

- CZP administered sc at the loading dose of CZP 400mg Q2W at Weeks 0, 2 and 4 followed by CZP 200mg Q2W (starting at Week 6)
- Placebo

At on-site visit days (at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50), the double-blind study treatments (including placebo) will be administered sc at the study site. At the Week 0, 2, 4, 6, and 8 visits, the administration must be done by dedicated, unblinded, and adequately trained site personnel. At the Week 10 and 12 visits, the subject will receive training on self-injection and the study treatment will be self-administered under the supervision of the unblinded study personnel. At Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 50, the study treatment administration should preferably be done by the unblinded study personnel, or alternatively by self-injection of the subject under the supervision of the unblinded study personnel.

Subjects who discontinue the double-blind study treatment and enter open-label treatment with CZP will be assessed 2 and 4 weeks after open-label CZP treatment has been initiated and every 12 weeks thereafter. Alternatively, subjects who discontinue the double-blind study treatment and receive other treatment (including biologics) will be assessed every 12 weeks after initiation of the other treatment. In either alternative schedule, assessments should be conducted until as close as possible to Week 52 (within ± 4 weeks), where Week 52 is relative to the original randomization at Week 0. Subjects will then be invited to the Week 52 assessment visit.

Period 3 (Follow-up period) - All subjects not participating in the SFE period after Week 52, including those withdrawn from the study prematurely, will have a single Follow-up visit, 8 weeks after Week 52/WD visit (10 weeks after their last administration of study medication).

SFE Period - Week 52 to Week 156, open-label:

At the completion of the Week 52 visit assessment, subjects on double-blind study treatment may receive open-label CZP treatment for an additional 2 years. Subjects who withdrew from double-blind study treatment and transitioned to open-label CZP treatment are also eligible to participate in the SFE period after completing the Week 52 visit assessment. Subjects on other treatments are not eligible to participate in the SFE period.

Eligible subjects are allowed to roll-over to the SFE-period up to 3 months after completion of the Week 52 assessments.

Starting at Week 64, all subjects are to visit the site approximately every 12 weeks for assessments. The last dosing visits will be at Week 154. The final study assessments are performed at Week 156.

The schedule of study assessments is provided in Section 5.2 of the protocol.

A schematic diagram of the study design is provided in Section 5.3 of the protocol.

Change #7

Section 2.3.2:

For each subject, the study will last a maximum of 66 weeks, as follows:

- Up to 6 weeks in the Screening period
- 52 weeks in the double-blind period
- A Follow-up visit, 8 weeks after Week 52/WD visit, 10 weeks after last dose administration (ie, Week 50, if the subject completed the entire dose administration schedule)

Has been changed to:

For each subject, the first 3 periods of the study will last a maximum of 66 weeks, as follows:

- Up to 6 weeks in the Screening period
- 52 weeks in the double-blind period
- A Follow-up visit, 8 weeks after Week 52/WD visit, for subjects not participating in the SFE Period.

For subjects participating in the SFE period, the study will extend up to a maximum of 104 additional weeks.

Change #8

Section 2.3.3:

The end of the study is defined as the date of the last visit (including Follow-up visit) of the last subject in the study.

Has been changed to:

The end of the study will be defined as the date of the last subject's last visit, defined as the Follow-up Visit 8 weeks after Week 52/WD visit for subjects not participating in the SFE Period, or the last visits of the SFE Period.

Change #9

Section 2.3.3:

The end of the study is defined as the date of the last visit (including Follow-up visit) of the last subject in the study.

Has been changed to:

The end of the study is defined as the date of the last visit (including Follow-up visit and SFE period) of the last subject in the study. Period start and ends are defined in Section 3.2.1.

Change #10

Section 2.3.4:

Approximately 900 subjects are expected to enter the Screening period in order to have 300 subjects randomized into the double-blind period. It is planned to enroll the subjects at approximately 95 sites.

Has been changed to:

Approximately 1200 subjects are expected to enter the Screening period in order to have 300 subjects randomized into the double-blind period. It is planned to enroll the subjects at approximately 120 sites.

Change #11

Section 2.3.6:

Subjects who are MRI-/CRP- are not eligible for randomization. The IVRS will be designed to ensure that at least 20% and no more than 40% of the randomized subjects belong to one of the three clinical subgroups above.

Has been changed to:

Subjects who are MRI-/CRP- are not eligible for randomization. The interactive response system (IXRS) will be designed to ensure that at least 20% of the randomized subjects belong to one of the three clinical subgroups above.

Change #12

Section 3.2.1.2:

The double-blind treatment period begins at the Baseline visit (Week 0) at the time of first study medication administration (inclusive) and ends at Week 52/WD visit. The Follow-up visit will take place 10 weeks after the last dose of study medication, which will be 8 weeks after the Week 52 vistis (if the Week 52 is the last non Follow-up visit) or less than 10 weeks after the W/D visit (if the W/D visit is the last non Follow-up visit).

Premature withdrawal visit assessments will be assigned to the next scheduled visit following the last visit where assessments are available. All visit measurements, even violating the visit window, will be utilized for the respective visit as long as they are in the proper sequence.

Subjects will be classified as completing the study if they complete the Week 52 Visit without early withdrawal of the study. This is regardless of whether they attend the Follow-up visit and regardless of whether they are on double-blind treatment, open-label CZP, or other treatment.

Has been changed to:

The double-blind treatment period begins at the Baseline visit (Week 0) at the time of first study medication administration (inclusive) and ends when:

- the subject completes the Week 52 visit on double-blind treatment, for subjects continuing into the Follow-up period
- the subject takes their loading dose/first dose of open-label CZP in the SFE period, for subjects completing the Week 52 visit on double-blind treatment and continuing into the SFE
- the subject takes their first dose of open-label CZP or other treatment (if prior to Week 52 visit)
- the subject discontinues (WD visit) and does not fall into the above categories.

For subjects who prematurely withdraw from the study prior to Week 52 (for example, those who cease to have double-blind and open-label visit data collected), their visit assessments at withdrawal will be assigned to the next scheduled visit following the last visit where assessments are available according to each protocol activity. This could be the next double-blind or open-label visit. All visit measurements, even violating the visit window, will be utilized for the respective visit as long as they are in the proper sequence.

Subjects will be classified as completing the study if they complete the Week 52 visit without early withdrawal of the study. This is regardless of whether they attend the Follow-up visit or

enter SFE period and regardless of whether they are on double-blind treatment, open-label CZP, or other treatment.

Change #13

Section 3.2.1.3:

The first day of the open-label period starts when a subject has discontinued the double-blind treatment period and they take their first dose of open-label CZP or other therapy. The open-label period ends when the subject discontinues the study.

Has been changed to:

The first day of the open-label period starts when a subject has discontinued the double-blind treatment period prior to Week 52 and they take their first dose of open-label CZP or other treatment. The open-label period ends when:

- the subject completes the Week 52 visit on open-label CZP or other treatment, for subjects continuing into the Follow-up period
- the subject takes their loading dose/first dose of open-label CZP in the SFE period, for subjects continuing into the SFE
- the subject discontinues the study (WD visit) and does not fall into the above categories.

Change #14

The following two sections have been added:

3.2.1.4 Follow-up period

For patients not entering the SFE period (no SFE informed consent), the Follow-up period will start on the day after the Week 52 visit (for subjects having Week 52 visit on double-blind or open-label therapy) or on the day after the WD visit. The Follow-up period will end on the Follow-up visit date. The Follow-up visit will take place 10 weeks after the last dose of study medication, which will be 8 weeks after the Week 52 visit (if the Week 52 is the last non-Follow-up visit) or less than 10 weeks after the WD visit (if the WD visit is the last non-Follow-up visit).

3.2.1.5 SFE period

The SFE period starts when the subject takes their loading dose/first dose of open-label CZP in the SFE period. The SFE period ends when the subject discontinues the study.

Change #15

Section 3.2.2:

The relative day will be included in different listings and will be calculated as follows:

- If the start (stop) date occurred on or after the first dose, but prior to the double-blind drug stop date, relative day is calculated as start (stop) date minus first dose date + 1.
- If the start (stop) date occurred after the last dose of double-blind drug, the relative day to the most recent dose is calculated as start (stop) date minus most recent dose date. The relative day in this situation should be preceded by a '+'.

- If the start (stop) date occurred before the first dose, the relative day is calculated as start (stop) date minus first dose date. The relative day in this situation should be preceded by a '-'.

For AEs, relative days for start and stop dates will be calculated as the number of days since the first injection of the medication. For non-treatment emergent AEs, relative day of onset will be negative if the event started and stopped before the first dose. Relative day will only be computed for fully completed dates and will be missing for partial dates.

Has been changed to:

The relative day will be included in the listings and will be calculated as follows:

- If the start (stop) date occurred on or after the first dose, and on or prior to the double-blind drug stop date, relative day is calculated as start (stop) date minus first double-blind dose date + 1. Relative day will be prefixed by a 'd' in the listings to show it's relative to double-blind treatment.
- For patients not entering the open-label CZP period (including SFE period), if the start (stop) date occurred after the last dose of double-blind drug, the relative day to the most recent double-blind dose is calculated as start (stop) date minus most recent double-blind dose date. The relative day in this situation should be preceded by a 'd+'.
- For subjects entering the open-label CZP period (including SFE period), if the start (stop) date occurred on or after the first open-label CZP start date, and on or prior to the open-label CZP stop date (including SFE period), relative day is calculated as start (stop) date minus first open-label dose date + 1. The relative day in this situation should be preceded by a 'o'.
- .For subjects entering the open-label CZP period (including SFE period), if the start (stop) date occurred after the last dose of open-label CZP drug, the relative day to the most recent open-label CZP dose is calculated as start (stop) date minus most recent open-label CZP dose date. The relative day in this situation should be preceded by a 'o+'
- If the start (stop) date occurred before the first dose, the relative day is calculated as start (stop) date minus first dose date. The relative day in this situation should be preceded by a 'd-'.

Relative day will only be computed for fully completed dates and will be missing for partial dates. For AEs, relative days for start and stop dates will be calculated as the number of days since the first injection of the relevant double-blind or open-label CZP medication. For non-treatment emergent AEs, relative day of onset will be negative if the event started and stopped before the first dose.

Change #16

Section 3.5.5:

The Per-Protocol Set (PPS) will consist of subjects in the FAS without any important protocol deviations that may influence the validity of the data for the primary efficacy variable. Treatment compliance as defined in Section 7 may also be utilized. Important protocol deviations will be predefined and evaluated at the data evaluation meeting prior to study unblinding database lock.

Has been changed to the following and Section 3.5.6 added:

The Per Protocol Set (PPS) will consist of subjects in the FAS without any important protocol deviations that may influence the validity of the data for the primary efficacy variable. Treatment compliance as defined in Section 7 may also be utilized. Important protocol deviations will be predefined and evaluated at the DEM prior to study unblinding at the Week 52 interim database lock. Protocol deviations occurring after Week 52 (for example, for subjects continuing in the SFE period) will not be considered for PPS impact as they occurred after assessment of the primary variable was performed.

3.5.6 SFE Safety Set

The SFE Safety Set (SFE-SS) will be defined as all subjects who continued into the SFE Period and who received at least 1 dose of CZP in the SFE Period. Safety data recorded during the SFE will be presented alongside the Week 52 analyses and hence it is not expected that this analysis set will be required.

Change #17

Section 3.6:

In general, for by visit data collected during the open-label period, subjects will be presented according to the treatments received in the double-blind period (CZP 200mg Q2W and PBO).

Concomitant medications will be summarized according to whether they were taken: during the double-blind period by CZP 200mg Q2W or PBO, or during the open-label period by PBO->OL CZP (patients who were randomized to PBO and then received open-label CZP), CZP->OL CZP (patients who were randomized to CZP and then received open-label CZP), or by the open-label other treatments group. In addition, concomitant medications taken during any CZP medication period (Total CZP) and all concomitant medications (All subjects) will also be summarized. See Section 6.4 for more detail.

AEs will be assigned to periods based on whether they started during the double-blind, open-label CZP or open-label other treatment. AEs will be summarized for the double-blind period by CZP 200mg Q2W or PBO, for the open-label CZP period by PBO->OL CZP or CZP->OL CZP (as above), by the open-label other treatments and by Total CZP (includes randomized CZP 200mg Q2W and AEs starting in the open-label CZP period). See Section 11.2 for more detail.

Has been changed to:

In general, for by visit data collected during the open-label period, subjects will be presented according to the treatments received in the double-blind period (CZP 200mg Q2W and PBO). For the by visit data collected during the SFE period, subjects will be presented in a single CZP 200mg Q2W treatment group.

Concomitant medications will be summarized according to whether they were taken: during the double-blind period by CZP 200mg Q2W or PBO, or during the open-label period by PBO->OL CZP (subjects who were randomized to PBO and then received open-label CZP), CZP->OL CZP (subjects who were randomized to CZP and then received open-label CZP), or by the open-label other treatments group. In addition, concomitant medications taken during any CZP medication period (Total CZP) and all concomitant medications (All subjects) will also be summarized. See Section 6.4 for more detail.

AEs will be assigned to periods based on whether they started during the double-blind, open-label CZP, open-label other treatment, or SFE periods. AEs will be summarized as follows:

- Double-blind period by CZP 200mg Q2W or PBO,
- Open-label CZP period by PBO->OL CZP or CZP->OL CZP (as above),
- Open-label other treatment period,
- SFE period by OL CZP
- Total CZP (includes randomized CZP 200mg Q2W, AEs starting in the open-label CZP period and AEs starting in the SFE period).

See Section 11.2 for more detail.

Change #18

Section 3.9:

Not applicable

Has been changed to:

The protocol stated that ADAb concentrations above 2.4 unit/ml would be defined as ADAb positive. However, during the trial it was noted that the background sample noise could only be determined during the sample analyses and hence the cut point cannot be pre-specified. Therefore the immunogenicity sections of the SAP were updated to define ADAb positive as being greater than a defined cut point. The cut point used will be agreed after the sample analysis at the DEM prior to database lock and unblinding.

Change #19

Section 4.3:

No interim analysis is planned for this study.

Has been changed to:

An interim analysis is planned after the completion of the double-blind period of the last subject at Week 52. At this time, the database from the double-blind period will be locked, the treatment codes will be made available to relevant to the study reporting team and an interim study report will be written. The investigators and subjects will remain blind to the assigned CZP dose regimen of the double-blind period. After the completion of the SFE period of the last subject, the database will be locked, and a final study report will be written. From the Week 52 visit onward, subjects will be treated with open-label CZP until the last dosing visit of the study (SFE Week 104).

Change #20

Section 4.2.2:

- Last Observation Carried Forward (LOCF): If there is missing data at the double-blind time point of interest, the last available post-Baseline measurement will be carried forward to that time point (including any previous scheduled or unscheduled visits). Observations will be

carried forward to all missing visits up until the time point of interest even if the subject has withdrawn from the study or entered the open-label period. This will not apply for the analysis of SI joint SPARCC score at Week 12 since there are no measurements collected between Baseline and Week 12.

Has been changed to:

- Last Observation Carried Forward (LOCF): If there is missing data at the double-blind time point of interest, the last available post-Baseline measurement will be carried forward to that time point (including any previous scheduled or unscheduled visits in double-blind or open-label periods). Using the date that the observation was recorded, data will be carried forward to all missing double-blind visits up until the time point of interest even if the subject has withdrawn from the study or entered the open-label period. For example, a subject withdrawing from double-blind at Visit 14 /Week 24 and entering open-label CZP will proceed to have a open-label visits at weeks 0, 2 and 4 post double-blind withdrawal followed by assessments every 12 weeks until 52 weeks post randomization. Using the date of the open-label visits, the number of weeks post randomization will be calculated to allow data to be carried forward to all subsequent missing double-blind visits. This will not apply for the analysis of SI joint SPARCC score at Week 12 since there are no measurements collected between Baseline and Week 12.

Change #21

Section 4.2.4:

The following sentence was added: If time of study treatment and time of event or concomitant medication is available and non partial then it will also be used however if missing or partial, only the dates will be compared.

Change #22

Section 4.3:

No interim analysis is planned for this study.

Has been changed to:

An interim analysis is planned after the completion of the double-blind period of the last subject at Week 52. The timing of the analysis will be when the last subject completes Week 52 visit in accordance with the double-blind, open-label CZP or open-label other treatment schedule. At this time, all visit based data from the double-blind period up to and including Week 52 visit, all open-label visit based data up to Week 52 visit, all available Follow-up data for patients already completing the study, all hospitalization/emergency room visit and health care provider consultation data, all study medication discontinuation and all prior and concomitant medication data including concomitant medical procedures, will be locked. Subjects still on the study awaiting Follow-up visit or in SFE, will continue to have AEs, laboratory, vital sign, PK and physical examination data collected per schedule until completion of the Follow-up or SFE period, at which point they will complete the study termination eCRF page. At the time of the interim analysis Week 52 DB lock, adverse event data entered to date will be cleaned but not locked. This will allow ongoing adverse event entry during the Follow-up and SFE periods. The treatment codes will be made available to the study reporting team and an interim study report

will be written. All tables, listings and figures described in this SAP will be produced at the time of the Week 52 DB lock. The Investigators and subjects will remain blind to the assigned CZP dose regimen of the double-blind period.

After the last subject has completed the SFE period, the database will be fully locked, and a final study report will be written. For subjects in the SFE period, from the Week 52 visit onward, subjects will be treated with open-label CZP until the last dosing visit of the study (SFE Week 104). During this time, only adverse events and study drug dispensation information will be collected in addition to the study termination data at completion or early withdrawal. Therefore, at the final DB lock, only the following tables and listings will be produced.

- Table 1.1.2: Disposition of Subjects Screened
- Table 1.2.2: Number of Subjects Completing each Visit
- Table 1.3: Disposition of Analysis Sets
- Table 1.4: Important Protocol Deviations
- Table 7.1: Extent of Exposure
- All tables in section 8 (adverse events, 31 tables in total with the exception of tables counting AEs reported after starting a new biologic, changing NSAIDs, changing DMARDs, or adding oral corticosteroids).
- Listing 1.2: Subject Disposition
- Listing 1.3: Study Termination
- Listing 1.4: Visit Dates
- Listing 3.1: Important Protocol Deviations
- Listing 4.1: Subject Analysis Sets
- All listings in section 7 (adverse events, 6 listings in total)

Note that if a substantial number of subjects are still awaiting their Follow-up visit when the interim analysis Week 52 DB lock occurs (and are therefore not entering the SFE), vital sign, laboratory, PK and physical examination outputs may be updated prior to the SFE analysis to include the information collected at the Follow-up visit.

Change #23

Section 4.6:

Other than the planned analyses based on the PPS, no other efficacy subsets are defined for statistical analyses.

Has been changed to:

The Randomized Set will be used to evaluate all subjects who were randomized to double-blind study medication. This analysis set will provide additional information on the efficacy analysis by describing findings in the full set of subjects who were randomized and will not exclude those who did not receive at least 1 dose of study medication or did not have a valid Baseline efficacy measurement for ASDAS.

Other than the planned sensitivity analyses based on the PPS and Randomized Set, no other efficacy subsets are defined for statistical analyses.

Change #24

Section 4.8:

Subgroups for age (<45 and ≥45 years), gender (male, female), race (white, other), symptom duration (<5, ≥ 5 years), tobacco use (never, current former), HLA-B27 genotype (positive, negative), region (North America, Europe, Asia), prior anti-TNF exposure (yes, no), anti-CZP antibody status (>2.4 units/mL at any post-Baseline assessment, ≤2.4 units/mL at all post-Baseline assessments), and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) will be utilized for summarizing the primary efficacy variable. Only summary statistics will be presented.

Has been changed to:

Subgroups for age (<45 and ≥45 years), gender (male, female), race (white, other), symptom duration (<5, ≥ 5 years), tobacco use (never, current former), HLA-B27 genotype (positive, negative), region (North America, Europe, Asia), prior anti-TNF exposure (yes, no), subjects with/without relevant changes to background medication, anti-CZP antibody status (positive, negative as defined in Section 10), and MRI/CRP classification (MRI+/CRP+; MRI+/CRP-; MRI-/CRP+) will be utilized for summarizing the primary efficacy variable. Only summary statistics will be presented.

Change #25

Section 6.2

- back pain of ≥ 3 month duration and age of onset < 45

Has been changed to:

- back pain of ≥ 3 month duration and age of onset < 45 (and per inclusion criteria back pain of ≥ 12 month duration and age of onset < 45)

Change #26

Section 7

CR = # actual syringes / # expected syringes

The second approach defines compliance with study drug administration based upon comparing the actual day of administration with the expected day of administration. The expected day of administration will be based upon the Baseline date. The sum of the absolute difference in days between the actual and expected days will be summarized. In addition, a ratio of compliance will be further computed based upon the actual and expected day. The ratio of compliance will also be summarized as a continuous variable and categorically (<0.80, ≥0.80-≤1.0 and >1.0). The general formula for the compliance ratio is given as follows:

CR = (Study Duration - Cumulative Difference) / Study Duration

The CR ranges between 0 and 1.

To calculate study duration, the date of the Week 50 visit or the last injection date prior to study treatment discontinuation will be compared to the Baseline date, as shown below:

Study Duration (days) = Week 50 visit/last injection date – Baseline date (maximum value is 350 days)

Has been changed to:

CR for syringes = # actual syringes / # expected syringes

The second approach defines compliance with study drug administration based upon comparing the actual day of administration with the expected day of administration. The expected day of administration will be based upon the Baseline date. The sum of the absolute difference in days between the actual and expected days will be summarized. In addition, a ratio of compliance will be further computed based upon the actual and expected day. The ratio of compliance will also be summarized as a continuous variable and categorically (<0.80, ≥0.80-≤1.0). The general formula for the compliance ratio is given as follows:

CR for injection day = (Study Duration - Cumulative Difference) / Study Duration

The CR for injection day ranges between 0 and 1.

To calculate double-blind study duration, the date of the Week 50 visit or the last injection date prior to double-blind study treatment discontinuation will be compared to the Baseline date, as shown below:

Double-blind Study Duration (days) = Week 50 visit/last injection date – Baseline date (maximum value is 350 days)

Change #27

Section 8

All efficacy analyses will be performed using the FAS. The PPS will be used for a sensitivity analysis on the primary endpoint only.

Has been changed to:

All efficacy analyses will be performed using the FAS. The PPS and Randomized Set will be used for a sensitivity analysis on the primary endpoint only (using the composite endpoint analysis).

Change #28

Section 8.1.3

The logistic regression analyses of the composite endpoint for ASDAS-MI responder rates at Week 52 (as described in Section 8.1.2) will also be repeated using the PPS.

Has been changed to:

The logistic regression analyses of the composite endpoint for ASDAS-MI responder rates at Week 52 (as described in Section 8.1.2) will also be repeated using the PPS and the Randomized Set.

Change #29

Section 8.3.1.10

The observed data at Week 52 will be used and analyzed according to randomized treatment, regardless of whether or not the subject is still on his/her randomized double-blind study treatment at that time.

Has been changed to:

The observed data at Week 52 will be used and analyzed according to randomized treatment, regardless of whether or not the subject is still on his/her randomized double-blind study treatment at that time. For example, subjects on open-label CZP or open-label other treatment at the time of their Week 52 visit will have that data included in the analysis including observed data at Week 52.

Change #30

Section 8.2.3

Sensitivity analyses of the secondary binary efficacy variables (ASAS40 at Weeks 12 and 52) as described in Section 8.2 will be as follows:

- Including observed data at Week 52 (or Week 12 as applicable): As described for the primary efficacy variable in Section 8.1.3.1.

Has been changed to:

Sensitivity analyses of the secondary binary efficacy variables (ASAS40 at Weeks 12 and 52) as described in Section 8.2 will be as follows:

- Including observed data at Week 52 (or Week 12 as applicable): As described for the primary efficacy variable in Section 8.1.3.1. It is possible that a subject completes the double-blind Week 12 visit and withdraws at this visit onto open-label, such that they complete an open-label Week 12 visit in addition. For any visits with data collected at the same visit but in multiple periods, the double-blind visit data will be used in preference to the open-label CZP data which will be used in preference to the open-label other treatment data.

Change #31

Section 8.3.1.10

The SF 36 section was re-written to use the QualityMetric Health Outcomes™ Scoring Software instead of the Ware et al, 2007 scoring algorithm.

Change #32

Section 9.1 paragraph 1

Certolizumab pegol plasma concentration data will be summarized by treatment group overall, and by antibody status, for each visit at which samples were taken, for the SS.

Has been changed to:

Certolizumab pegol plasma concentration data will be summarized by treatment group overall, and by Anti-CZP antibody (ADAb) status of individual subjects (as defined below), for each scheduled visit at which samples were taken, for the SS. Samples collected out of window may

be excluded from the analysis. The final decision will be determined at the DEM meeting prior to database lock.

Change #33

Section 9.1 paragraph 3

Individual plasma concentrations for CZP, and anti-CZP levels versus time will be produced on the same graph. The Y-axis on the left will represent the CZP and the Y-axis on the right will show the anti-CZP levels (units/mL).

Has been changed to:

Individual subject plasma concentrations for CZP, anti-CZP levels, ASDAS scores and dose levels versus time will be produced on the same graph. Two Y-axes on the left will represent the CZP concentrations and anti-CZP levels. The Y-axis on the right will show the ASDAS score. The x-axis will represent time (weeks) with lines showing the treatment and dose.

Change #34

Section 10:

Frequency tables of anti-CZP antibody (ADAb) status by visit will be presented for the SS.

The number and percentage of subjects with anti-CZP antibody concentrations above 2.4 units/mL will be reported as follows:

- Number and percentage of subjects with ADAb >2.4 units/mL at the time of each visit
- Number and percentage of subjects with ADAb >2.4 units/mL at any visit during treatment (not including post treatment withdrawal or Follow-up visits)
- Number and percentage of subjects with ADAb >2.4 units/mL at any visit including post treatment withdrawal and Follow-up visits.

For the subgroup of subjects with at least 1 anti-CZP antibody level above 2.4 units/mL, the time point of occurrence of the first finding will also be displayed.

Has been changed to:

Anti-CZP antibody (ADAb) status will be determined for each visit where samples were taken. A cut point used to define ADAb negative and positive will be agreed after the sample analysis at the data evaluation meeting (DEM) prior to database lock and unblinding.

In additional, ADAb status of individual subjects will be determined and summarized using the same cut point:

- ADAb positive is defined as having a value > a defined cut point while on CZP treatment
- ADAb negative is defined as having no values > a defined cut point while on CZP treatment

The above definitions will be used for subgroup analyses by anti-CZP antibody status. Note that "while on CZP treatment" in the previous definitions refers to measurements taken when the subject is exposed to CZP study treatment. Measurements at Baseline, at the Follow-up, and at any visit >70 days after last CZP dose are not included in this algorithm.

Note that for purposes of classifying a subject as negative or positive for anti-CZP antibodies, the value must be above the defined cut point and must occur after the subject has had at least one injection of CZP. By definition, a subject cannot be positive for anti-CZP antibodies if they have only received PBO, regardless of how high the value may be. However, a subject randomized to PBO and escaping to CZP may become positive based on values during the OL period while receiving CZP.

A frequency table of anti-CZP antibody status by visit will be presented. In addition, the first occurrence of anti-CZP antibody positive will be tabulated by visit including the cumulative count. That is, each anti-CZP antibody positive subject will be counted only once at the visit where anti-CZP antibody positivity was first observed. The table will also include a summary of the total number of anti-CZP antibody and the total number of positive results observed on treatment (at any visit during treatment not including post treatment withdrawal or Follow-up visits) and at any visit including post treatment withdrawal and Follow-up visits.

Change #35

Section 11.1:

Exposure to the open-label CZP treatment will also be calculated using the above 4 methods considering only dosing during the time the patient is receiving open-label CZP study medication. Exposure to open-label other treatments will not be calculated.

For the first 3 approaches, tables will summarize exposure days for the placebo, CZP 200mg Q2W andopen-label CZP treatment groups.

Has been changed to:

Exposure to the open-label CZP treatment will also be calculated using the above 4 methods considering only dosing during the time the subject is receiving open-label CZP study medication prior to Week 52 visit. Exposure during the SFE period will be calculated using methods 2, 3 and 4 assuming first dose in the SFE period starts when the subject takes their loading dose/first dose of open-label CZP in the SFE period and ends when the subject has their last administration of study medication (or if missing, the date of withdrawal). Total CZP exposure will be calculated using all 4 methods, by summing the exposure to CZP during the double-blind, open-label CZP and SFE periods. Note that for method 1, the SFE period will be excluded from the Total CZP as data is not collected on dose administration. Exposure to open-label other treatments will not be calculated.

For the first 3 approaches, tables will summarize exposure for the placebo, CZP 200mg Q2W, open-label CZP treatment groups (split by the treatment taken during the double-blind period), SFE open-label CZP and Total CZP.

Change #36

Section 11.2

AE start dates will be examined to determine if they are treatment-emergent and attributable to the double-blind treatment period or open-label period. AEs occurring either before double-blind study drug administration (pre-treatment) or outside of the windows described below will be defined as non-treatment emergent.

Table 11-1: Assignment of Adverse Events to Study Periods		
Type of Subject	**Assignment Rule Based on AE Start Date**	**Assignment**
Subjects who participate only in the double-blind period	Start date is on or after first study drug administration during the double-blind period and before the last study drug administration + 70 days.	Double-blind treatment-emergent
Subjects who enter the open-label period prior to Week 52	1. Start date is on or after first study drug administration during the double-blind period and before the start date of open-label CZP or other treatment.	Double-blind treatment-emergent
	2. Start date is on or after the start date of open-label CZP and before the start date of open-label other treatment.	Open-label CZP
	3. Start date is on or after the start date of open-label other treatment.	Open-label other treatment

If AE intensity or relationship is missing, then the given event will be imputed as severe or related, respectively.

The frequency of all AEs including TEAEs will be presented for each treatment group separately by System Organ Class, high level term, and preferred term. The data will be displayed as number of subjects experiencing the AEs, percentage of subjects, and number of AEs. Certain summaries will also include exposure-adjusted incidence rates and event rates. Only TEAEs occurring in the double-blind period and open-label period will be presented.

The following AE summaries will be presented:

- Overview of TEAE
- TEAE
- Serious TEAE
- Non-serious TEAE
- TEAE with fatal outcome
- TEAE leading to permanent withdrawal of study medication
- Severe TEAE (included in TEAE table by intensity)
- Drug-related TEAE (included in TEAE table by relationship)
- Serious TEAE by relationship
- Non-serious TEAE by relationship
- Fatal TEAE by relationship

- Injection reactions (Injection site reactions, systemic injection reactions, acute systemic injection reactions, and delayed systemic injection reactions)
- TEAE of special interest (see below)
- TEAE sorted by incidence of PTs in the CZP 200mg group (SOC and HLT will not be utilized)
- Non-serious TEAE with an incidence of at least 5% in 1 of the 2 randomized groups (HLT will not be utilized)
- Non-serious TEAE with an incidence of at least 5% in 1 of the 2 randomized groups by relationship (HLT will not be utilized)
- TEAE subject numbers

The AEs of interest and the approach for summarizing them are described below:

3. Serious infections, including opportunistic infections. Serious infections will be summarized using the Serious TEAE table. No separate table is planned. In addition, opportunistic infections (including tuberculosis) will be presented in a table using UCB-defined search criteria.
4. Malignancies, including lymphoma. These will be presented in 2 tables using the criteria SMQ = "Malignant or unspecified tumours" and SMQ="Malignancies", respectively.
5. Congestive heart failure. These will be manually identified by the study physician from the TEAE table. No separate table is planned. In addition, major adverse cardiac events (MACE) will be presented in a table using UCB-defined search criteria and will include fatal and serious non-fatal myocardial infarction, cerebrovascular events and congestive heart failure.
6. Demyelinating-like disorders. These will be manually identified by the study physician from the previously described TEAE table. No separate table is planned.
7. Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia. These will be presented in a table using the criteria SMQ = "Haematopoietic cytopenias" in the subset of SAEs.
8. Serious bleeding events. These will be presented in a table using the criteria SMQ = "Haemorrhages" in the subset of SAEs.
9. Lupus and lupus-like illness. These will be manually identified by the study physician from the TEAE table. No separate table is planned.
10. Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, anderythema multiforme). These will be manually identified by the study physician from Serious TEAE table. No separate table is planned.

The tables for 1, 2, 3, 5, and 6 above will include the incidence rate with associated 95% CI, and the exposure adjusted event rate.

Although not an AE of interest, hepatic events will also be summarized. They should be identified using the following 5 SMQs: Cholestasis and jaundice of hepatic origin; Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions; Hepatitis,

noninfectious; Liver-related investigations, signs and symptoms; and Liver-related coagulation and bleeding disturbances.

Because subjects will be able to adjust background medications during the study, some additional AE tables will be prepared in which events occurring while on certain background medications will be summarized. The list of these supportive tables is as follows:

- TEAEs reported after starting a new biologic, but within 10 weeks of stopping CZP
- TEAEs reported one month after changing NSAID type
- TEAEs reported three months after changing or adding a DMARD
- TEAEs reported within one month of an addition of oral corticosteroids or 50% increase in dose

The purpose of these tables will be to assess whether any observed treatment differences in the AE profile may be due, in part, to these prespecified background medications.

A TEAE table will also be presented for the 'anti-CZP antibody status' subgroup. Only the subjects exposed to CZP in the double-blind period will be considered and the double-blind TEAEs will be displayed by the antibody status (negative, positive as defined in section 10). A further positive column will be presented by summarizing the TEAEs occurring after the onset of the positive antibody status. The incidence rate will be presented in addition to the associated 95% CI, and the exposure adjusted event rate.

The TEAE incidence rates will also be adjusted for exposure (as calculated using methods 3 and 4 in Section 11.1) and reported by 100 patient-exposure years. Two approaches will be applied to adjust for exposure. One will only use the first occurrence of an AE with corresponding exposure (exposure-adjusted incidence rate [EAIR]) and the second approach will use all AEs and the entire exposure (exposure-adjusted event rate [EAER]).

For the EAIR, the first occurrence of an TEAEs for a certain treatment group will be utilized (either placebo or CZP 200mg Q2W for the double-blind period or open-label CZP) and divided by the sum of exposure of all subjects in the respective treatment group, where subjects experiencing the respective AE will be censored at the time of occurrence of the AE. The EAIR will be multiplied by a factor of 100 to give a rate per 100 patient-years.

For the EAER, all TEAEs for a certain treatment group will be utilized (either placebo or CZP 200mg Q2W for the double-blind period or open-label CZP) and divided by the sum of exposure of all subjects in the respective treatment group. The EAER will be multiplied by a factor of 100 to give a rate per 100 patient-years.

The summary of TEAEs, serious TEAEs, and TEAEs leading to permanent withdrawal of study medication will include the EAIR (with corresponding 95% exact CI) and EAER. The confidence interval for the EAIR will be based on Poisson rate CIs. The bounds of the exact 95% CIs are estimated by

$$\text{lower bound} = \frac{1}{2 \cdot t} \cdot \chi^2_{2 \cdot \text{number of patients with events}, 0.025} \quad \text{and} \quad \text{upper bound} = \frac{1}{2 \cdot t} \cdot \chi^2_{2 \cdot (\text{number of patients with events}+1), 0.975}$$

$\chi^2_{n,\gamma}$ denotes the chi^2-distribution with n degrees of freedom and quantile γ and t is the exposure censored at the time of occurrence of the AE.

Has been changed to:

AE start dates will be examined to determine if they are treatment-emergent and attributable to the double-blind period, open-label period or SFE period. AEs occurring either before double-blind study drug administration (pre-treatment) or outside of the windows described below will be defined as non-treatment emergent.

Table 11-1: Assignment of Adverse Events to Study Periods

Type of Subject	Assignment Rule Based on AE Start Date	Assignment
Subjects who do not enter the open-label period prior to Week 52 and do not enter SFE	Start date is on or after first study drug administration during the double-blind period and on or before the last study drug administration in the double-blind period + 70 days.	Double-blind TEAE
Subjects who do not enter the open-label period prior to Week 52 but do enter SFE after Week 52	Start date is on or after first study drug administration during the double-blind period and prior to loading dose/first dose administration in SFE	Double-blind TEAE
Subjects who enter the open-label period prior to Week 52	1. Start date is on or after first study drug administration during the double-blind period and before the start date of open-label CZP or other treatment.	Double-blind TEAE
	2. Start date is on or after the start date of open-label CZP and either before the start date of open-label other treatment (for subjects moving into open-label other treatment), or before the loading dose/first dose administration in SFE (for subjects moving into SFE period) or before the last study drug administration during the Open-label CZP period (prior to Week 52) + 70 days (for subjects who complete the Follow-up visit not entering SFE).	Open-label CZP TEAE
	3. Start date is on or after the start date of open-label other treatment.	Open-label other treatment TEAE

Table 11-1: Assignment of Adverse Events to Study Periods		
Type of Subject	**Assignment Rule Based on AE Start Date**	**Assignment**
Subjects who enter the open-label SFE period (Week 52 completers only)	Start date is on or after the loading dose/first dose administration in SFE.	SFE TEAE

If AE intensity or relationship is missing, then the given event will be imputed as severe or related, respectively.

The frequency of all AEs including TEAEs will be presented for each treatment group separately by System Organ Class, high level term, and preferred term. The data will be displayed as number of subjects experiencing the AEs, percentage of subjects, and number of AEs. Certain summaries will also include exposure-adjusted incidence rates and event rates. TEAEs will be summarized by treatment and period as described in Section 3.6.

The following AE summaries will be presented:

- Overview of TEAE
- TEAE
- Serious TEAE
- Non-serious TEAE
- TEAE with fatal outcome
- TEAE leading to permanent withdrawal of study medication
- Severe TEAE (included in TEAE table by intensity)
- Drug-related TEAE (included in TEAE table by relationship)
- Serious TEAE by relationship
- Non-serious TEAE by relationship
- Fatal TEAE by relationship
- Injection reactions (Injection site reactions, systemic injection reactions, acute systemic injection reactions, and delayed systemic injection reactions)
- TEAE of special interest (see below)
- TEAE sorted by incidence of PTs in the CZP 200mg group (SOC and higher level term [HLT] will not be utilized)
- Non-serious TEAE with an incidence of at least 5% in 1 of the 2 randomized groups (HLT will not be utilized)
- Non-serious TEAE with an incidence of at least 5% in 1 of the 2 randomized groups by relationship (HLT will not be utilized)
- TEAE subject numbers

The AEs of interest and the approach for summarizing them is briefly described below. Further information is provided in the guidance document (AEs of Interest – Cimzia Program 9February2017).

11. Serious infections, including opportunistic infections. Serious infections will be summarized using the Serious TEAE table. No separate table is planned. In addition, opportunistic infections (including tuberculosis) will be presented in a table using UCB-defined search criteria.
12. Malignancies, including lymphoma. These will be presented in 2 tables using the Standardized MedDRA Query (SMQ) criteria "Malignant or unspecified tumours" and "Malignant tumours" respectively.
13. Serious cardiovascular events. These will be presented in a table including all serious TEAEs with the SMQs of "Haemorrhagic central nervous system vascular conditions" and "Ischaemic central nervous system vascular conditions", including all serious TEAEs with the HLT of "Ischaemic coronary artery disorders" except events coding to PTs of "Chest Pain" or "Chest discomfort" and including all serious TEAEs with HLTs of "Heart Failures NEC", "Left Ventricular Failures", or "Right Ventricular Failures" and which also code to the SOC of "Cardiac Disorders".
14. Congestive heart failure. These will be manually identified by the study physician from the TEAE table. No separate table is planned.
15. Demyelinating-like disorders. These will be manually identified by the study physician from the previously described TEAE table. No separate table is planned.
16. Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia. These will be presented in a table using the criteria SMQ = "Haematopoietic cytopenias" in the subset of Serious TEAEs.
17. Serious bleeding events. These will be presented in a table using the criteria SMQ = "Haemorrhage terms (excl laboratory terms)" in the subset of Serious TEAEs.
18. Lupus and lupus-like illness. These will be manually identified by the study physician from the TEAE table. No separate table is planned.
19. Serious skin reactions (eg, Stevens-Johnson Syndrome, toxic epidermal necrosis, anderythema multiforme). These will be manually identified by the study physician from Serious TEAE table. No separate table is planned.

The tables for 1, 2, 3, 5, and 6 above, will include the exposure-adjusted incidence rate (EAIR) with associated 95% CI, and the exposure-adjusted event rate (EAER) as described below.

Although not officially AEs of interest, the following events will also be summarized as described in the AEs of Interest – Cimzia Program 9February2017 guidance document.

20. Hepatic events. These will consist of a subset of all TEAEs, identified using the following 5 SMQs: Cholestasis and jaundice of hepatic origin; Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions; Hepatitis, noninfectious; Liver-related investigations, signs and symptoms; and Liver-related coagulation and bleeding disturbances.

21. Hypersensitivity reactions and anaphylactic reactions. Hypersensitivity reactions will be summarized as any TEAEs occurring on the same day or the day after injection was received, which code to the following preferred terms: Administration site hypersensitivity, Documented hypersensitivity to administered product, Drug hypersensitivity, Hypersensitivity, Hypersensitivity vasculitis, Infusion site hypersensitivity, Injection site hypersensitivity, Medical device site, hypersensitivity, Type II hypersensitivity or Type IV hypersensitivity reaction. Anaphylactic reactions will be defined using an algorithmic approach as described in the "AEs of Interest – Cimzia Program 9February2017" guidance document.

Because subjects will be able to adjust background medications during the study, some additional AE tables will be prepared in which events occurring while on certain background medications will be summarized. The list of these supportive tables is as follows:

- TEAEs reported after starting a new biologic, but within 10 weeks of stopping CZP
- TEAEs reported one month after changing NSAID type
- TEAEs reported three months after changing or adding a DMARD
- TEAEs reported within one month of an addition of oral corticosteroids or 50% increase in dose

The purpose of these tables will be to assess whether any observed treatment differences in the AE profile may be due, in part, to these prespecified background medications.

A TEAE table will also be presented for the 'anti-CZP antibody status' subgroup defined in Section 10 . Only subjects exposed to CZP and only TEAEs occurring after first dose of CZP will be considered. A further column will be presented summarizing TEAEs occurring after the onset of the positive antibody status. The EAIR will be presented in addition to the associated 95% CI, and the EAER.

The TEAE incidence rates will also be adjusted for exposure (as calculated using methods 3 and 4 in Section 11.1) and reported by 100 subject years of exposure. 100 subject-years is defined as the sum of the exposure / number of subjects *100. Two approaches will be applied to adjust for exposure. One will only use the first occurrence of an AE with corresponding exposure (EAIR) and the second approach will use all AEs and the entire exposure (EAER).

For the EAIR, the first occurrence of an TEAEs for a certain treatment group will be utilized (either placebo or CZP 200mg Q2W for the double-blind period or open-label CZP) and divided by the sum of exposure of all subjects in the respective treatment group, where subjects experiencing the respective AE will be censored at the time of occurrence of the AE. The EAIR will be multiplied by a factor of 100 to give a rate per 100 subject-years.

For the EAER, all TEAEs for a certain treatment group will be utilized (either placebo or CZP 200mg Q2W for the double-blind period or open-label CZP) and divided by the sum of exposure of all subjects in the respective treatment group. The EAER will be multiplied by a factor of 100 to give a rate per 100 subject-years.

The summary of TEAEs, serious TEAEs, and TEAEs leading to permanent withdrawal of study medication will include the EAIR (with corresponding 95% exact CI) and EAER. The

confidence interval for the EAIR will be based on Poisson rate CIs. The bounds of the exact 95% CIs are estimated by

$$\text{lower bound} = \frac{1}{2 \cdot t} \cdot \chi^2_{2 \cdot \text{number of patients with events}, 0.025} \quad \text{and} \quad \text{upper bound} = \frac{1}{2 \cdot t} \cdot \chi^2_{2 \cdot (\text{number of patients with events}+1), 0.975}$$

$\chi^2_{n,\gamma}$ denotes the chi^2-distribution with n degrees of freedom and quantile γ and t is the exposure censored at the time of occurrence of the AE.

Change #37

Section 11.4.1:

The number and percent of subjects with abnormal vital sign values will be summarized by visit and for any visit.

Has been changed to:

The number and percent of subjects with abnormal vital sign values will be summarized by visit and for any visit. Abnormal vital sign results are defined as follows.

Table 11-2: Definition of Abnormal Vital Signs

Vital Sign Parameter	Abnormally Low	Abnormally High
Systolic Blood Pressure (mmHg)	<= 90 and decrease of >=20	>=180 and increase of >=20
Diastolic Blood Pressure (mmHg)	<=50 and decrease of >=15	>=105 and increase of >=15
Pulse Rate (bpm)	<=50 and decrease of >=15	>=120 and increase of >=15

Change #38

Section 11.4.3.3:

Physical examination will be performed at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 24, 36, 52/WD and at the Follow-up visit. Physical examination findings will be recorded in the CRF only at Screening. Physical examination data will be listed only.

Has been changed to:

Physical examination will be performed at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 24, 36, 52/WD and at the Follow-up visit (8 weeks after the Week 52/WD visit for subjects not participating in the SFE period). Physical examination findings will be recorded in the eCRF only at Screening. Physical examination data will be listed only.

14.3 AMENDMENT 3

Rationale for the amendment

The analysis plan was updated to ensure consistency with protocol amendment 4, which included the addition of ASQoL, Nocturnal spinal pain and Uveitis as secondary endpoints and an alternative primary endpoint and testing hierarchy for Canada (and any other country where applicable or where requested by Regulatory Authorities). All modifications are detailed below.

Change #1

General: Minor textual clarifications throughout about data handling for the SFE period.

Change #2

Sections 2.2, 4.2.1, 8, 8.1.3, 8.2.2, 8.2.2.1, 8.2.2.2, 8.2.3, 8.2.3.1, 8.2.3.2, 8.3.1.2 updated to correspond with protocol amendment 4. The following variables were updated:

- ASAS40 was added as the primary endpoint for Canada (and any other country where applicable or where requested by Regulatory Authorities), hence an alternative set of secondary endpoints and sequential testing hierarchy were provided.
- Secondary endpoint added: Change from Baseline in ASQoL at Week 52
- Secondary endpoint added: Change from Baseline in ASQoL at timepoints other than Week 52
- Secondary endpoint added: Change from Baseline in nocturnal spinal pain (NRS) at Week 52
- Secondary endpoint added: Number of subjects with Anterior Uveitis (AU) or new AU flares through Week 52

Change #3

Section: 2.2.3:

Anti-CZP antibody (ADAb) concentrations will be measured and summarized at Baseline, Weeks 1, 2, 4, 12, 24, 36, 52/WD, and the Follow-up visit (if applicable). In addition, the anti-CZP Ab concentrations will be assessed in subjects who withdraw from study drug and transition to open-label CZP. The number and percentage of subjects with anti-CZP antibody concentrations above a defined cut point will be reported as follows:

- Number and percentage of subjects with ADAb > defined cut point at the time of each visit
- Number and percentage of subjects with ADAb > defined cut point at any visit during treatment (not including post treatment withdrawal or Follow-up visit)
- Number and percentage of subjects with ADAb > defined cut point at any visit including post treatment withdrawal or Follow-up visit

The cut point to use will be agreed after the sample analysis at the data evaluation meeting (DEM) prior to database lock and unblinding.

Was changed to:

Anti-drug antibody (ADAb) (Anti-CZP antibody) concentrations will be assessed at Baseline and Weeks 1, 2, 4, 12, 24, 36, 52/WD, and the FU visit (8 weeks after the Week 52/WD visit). In

addition, the ADAb will be assessed in subjects who withdraw from double-blind study drug and transition to open-label CZP prior to Week 52.

Determination of ADAb will be done using a validated screening, confirmation and titration ADAb bridging assay, with potential further characterization by a neutralizing antibody assay. The immunogenicity data will be processed according to dedicated Bioanalytical Analysis plans.

The following variables will be analyzed as described in Section 10:

- Anti-CZP antibodies at Baseline, Weeks 1, 2, 3, 12, 24, 36 and 52/WD
- Status of ADAb (including overall, baseline and treatment-emergent classification)
- ADAb response characterized for their neutralizing potential

Change #4

Section 2.2.4.1 and 11.2: Summaries of the following were updated:

- Injection reaction summaries were removed.
- TEAEs with CZP incidence >=1% and CZP incidence>PBO incidence was added.
- Serious Cardiovascular and demyelinating-like disorder were updated to align to latest UCB standards.
- The following was changed to be optional: TEAEs reported after: new biologic, changing NSAID, changing DMARD or addition of oral corticosteroid.

Change #5

Section 3.1: The following paragraph was removed:

If imputation is being performed, which by definition results in all subjects having available data for analysis, then summary statistics will not present the 'n' (number of available measurements).

Change #6

Section 3.2.1.2, 3.2.1.3, 3.2.1.4, 3.2.1.5: Clarifications were made to the period definitions to ensure a clearer definition of the start and end of each period.

Change #7

Section 3.5.4: The Full Analysis Set (FAS) will consist of all subjects in the RS who have received at least 1 dose of study medication and have a valid Baseline efficacy measurement for ASDAS.

Was changed to:

The Full Analysis Set (FAS) will consist of all subjects in the RS who have received at least 1 dose of study medication.

Change #8

Section 3.6 and 11.2 : were updated to provide clarity on how Adverse events are assigned to study periods. An additional Total CZP AE summary was added that includes (includes randomized CZP 200mg Q2W and AEs starting in the open-label CZP period).

Change #9

Section 4.8 and 8.1.3: Baseline SPARCC scores (<5 and >=5) was added as a subgroup analyses. Anti-CZP antibody was removed and replaced with efficacy-antibody analysis in section 10. Data handling for subjects missing the 2nd screening CRP value was added.

Change #10

Section 6.1: Age groups were updated

Change #11

Section 6.4 was updated to clarify how concomitant medications are assigned to periods

Change #12

Section 7: Details for the derivation of Total expected syringes was added and the ratio of compliance categories were extended to present >1-<1.2 and >1.2.

Change #13

Section 8.1.1 and 8.1.3: Derivation of ASDAS-MI was updated to include handling of subjects with lowest score possible (0.636) post-baseline to include them as responders. A sensitivity analysis was added using the definition of improvement >=2.0 relative to Baseline alone.

Change #14

Section 8.1.3.2: Clarified that imputations would be limited to in range results and the MCMC would include measurements from the previous visit as explanatory variables in the model.

Change #15

Section 8.1.3.3: Tipping point deltas updated to vary for placebo and CZP subjects.

Change #16

Section 8.1.3.3: Due to ASAS40 now bring a primary analysis (for Canada), sensitivity analysis were added using methods similar to ASDAS-MI.

Change #17

Section 8.2.1.6 was added since ASQoL is now a secondary endpoint. The text was updated from: The ASQoL consists of 18 items, each with a score of 0 = no or 1 = yes, so that the sum score ranges from 0 to 18, with higher scores indicating worse quality of life. If three or fewer items are missing, the missing responses will be imputed with the mean of the available responses from that visit to calculate a total score. If more than three items are missing, the total score will be left missing.

To: The ASQoL, a validated disease-specific 18-item questionnaire, has been developed specifically for measuring HRQoL in subjects with AS (Doward et al, 2003). An nr-axSpA specific scoring algorithm is presently being developed, but it is unclear when this algorithm will

become available relative to the timing of the AS0006 database lock. Should this alternative scoring approach become available prior to finalization of the clinical study report, analyses of ASQoL data may be repeated using this alternate scoring approach appropriate for nr-axSpA population and methods will be described either in a SAP amendment or within the Documentation of Statistical Methods appendix to the study report.

Change #18

Section 8.2.1.7: Section added and text moved from Other endpoints for Nocturnal Spinal Pain since promotion to secondary endpoint.

Change #19

Section 8.2.2.1: The following text was added since Uveitis was promoted to a secondary endpoint. The number of subjects with new onset post-Baseline AU or new AU flares through Week 52 is a categorical secondary efficacy endpoint for all regions. Subjects will be classified as having post-Baseline Uveitis: a TEAE of Uveitis, a new diagnosis of Uveitis or a flare of uveitis at any visit post-Baseline which is on or before the Week 52 visit. All patients without evidence of uveitis events, new diagnosis or flares will be considered not to have post-Baseline Uveitis. As a dichotomous outcome variable, treatment groups will be compared for differences using logistic regression including treatment, region and MRI/CRP classification as explanatory variables. Subjects with no evidence of new AU flares will be considered as having no flare.

Change #20

Section 8.2.2.2: Step by step description of referenced-based multiple imputation was updated to allow use of the SAS® MNAR option in Proc MI available in version 9.4.

Change #21

Section 8.3: List extended to include EQ-5D which was missed in error. WPS nonparametric bootstrap-t method replaced with the more conventional MMRM analysis.

Section 8.3.1.12: LOCF removed for WPS analysis

Appendix 13.1: Non-parametric boostrap-t method was removed.

Change #22

Section 8.3.1.11: ASAS-NSAID analysis updated to summarize by periods using the start/end of concomitant medication dates. The following paragraph was added:

For the observed case analysis, only intervals that end on or prior to end of the double-blind treatment period will be included. For the LOCF analysis, all data will be included for all intervals up to Week 52 (1 year) irrespective of whether the subject is on double-blind or open-label study medication.

Change #23

Section 8.3.1.13: MOS sleep scale analysis updated to use QualityMetric Health Outcome scoring software.

Change #24

Section 9.1: The following paragraph was inserted to replace evaluation of evaluable PK data at the DEM meeting prior to DB lock. All CZP concentrations will be reviewed after unblinding by study statistician and clinical pharmacologist to ensure all values are plausible, and values deemed anomalous will be excluded from summary statistics.

Change #25

Section: 10: Immunogenicity analysis section was replaced with latest best practices.

Change #26

Section: 11.1: A Total CZP exposure summary was added that includes (includes randomized CZP 200mg Q2W and open-label CZP period but excludes SFE CZP).

Change #27

Section: 11.3: A shift table of liver function test change from baseline to maximum post-baseline category was added.

Change #28

Section: 11.4.3.4: A table of QuantiFERON-TB Gold Tuberculosis Test Results was added.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

Name: as0006-sap-amend-3

Version: 1.0

Document Number: CLIN-000119586

Title: AS0006 SAP Amendment 3

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