

## PROTOCOL AS0006 (C-AXSPAND) AMENDMENT 5

# 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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## 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-LD	Ankylosing Spondylitis Disease Activity Score low 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
ASpiMRI-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

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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

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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 <sup>®</sup>	Medical Dictionary for Regulatory Activities <sup>®</sup>
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

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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-FAS	Safety Follow-Up Full Analysis Set
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

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SPC	Summary of Product Characteristics
SS	Safety Set
SSCM	Single Safety Case Management
SSZ	sulfasalazine
STIR	short-tau-inversion recovery
TEAE	treatment-emergent adverse event
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 ( $\geq 18$  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)  $\geq 4$ , and spinal pain  $\geq 4$  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](#).

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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.

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## 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).

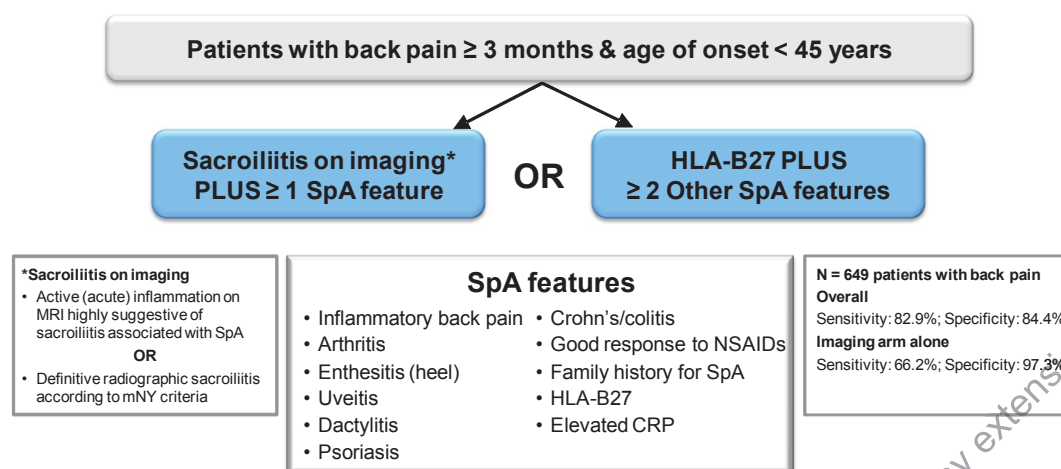
Several large observational and noninterventional cohort studies (Cuirena et al, 2013; Sieper and van der Heijde, 2013a) reported a similar burden of disease at study baseline across AS studies (captured through BASFI and BASDAI) in nonradiographic as well as radiographic axSpA (captured through BASDAI). 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  $\geq 2$  bilaterally or sacroiliitis grade 3 to 4 unilaterally PLUS at least 1 of the following clinical criteria: low back pain and stiffness for  $\geq 3$  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  $\geq 3$  months and age of onset <45 years, classification of axSpA can be made based on either evidence of sacroiliitis on radiographs or MRI plus  $\geq 1$  typical SpA feature or the presence of HLA-B27 plus  $\geq 2$  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. In addition, MRI assessment of SI joint structural damage and laboratory assessment for CRP will be performed, and data from selected efficacy variables will be collected at the end of the SFE Period. 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 and at Week 156 for selected variables:

- 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 Baseline in BASMI linear
- ASDAS disease activity (Ankylosing Spondylitis Disease Activity Score inactive disease [ASDAS-ID], Ankylosing Spondylitis Disease Activity Score low disease [ASDAS-LD; Machado et al, 2018], Ankylosing Spondylitis Disease Activity Score high disease activity [ASDAS-HD], Ankylosing Spondylitis Disease Activity Score very high disease activity

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[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 Week 156 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, Week 52, and Week 156
- 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

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## **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 Other biomarker 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], Desert 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)  $\beta$ , 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 Other 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  $-80^{\circ}\text{C}$  at the central biorepository for up to 20 years.

## **4.3 Other 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.

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## 4.4 Safety variables

### 4.4.1 Secondary safety variables

Assessment time points for safety variables are specified in [Table 5–1](#) and [Table 5–6](#). The secondary safety variables are as follows:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of serious adverse events (SAEs)
- Adverse events leading to withdrawal from investigational medicinal product (IMP)

### 4.4.2 Other safety variables

Other safety variables are assessed as specified in [Table 5–1](#) and [Table 5–6](#), and are as follows:

- Change from Baseline in vital signs (blood pressure, temperature, and pulse rate)
- Change from Baseline in clinical laboratory values (hematology, biochemistry, and urinalysis)

Physical examination findings considered clinically significant changes since the physical examination completed at the Screening Visit will be recorded as AEs.

## 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 latent tuberculosis (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  $\geq 2$  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  $\pm 4$  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 ( $\pm 2$  weeks) for-assessments.

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

### **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.

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## 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.

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

Visit #	Scr	Scr day -5 to -3	Assessments																													
			1/BL	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28		
Week Protocol Activity	-6 weeks to -1 day		0	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	FU	
PhGADA			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		
PGADA			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Productivity			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Resources utilization <sup>o</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X		
Genetics/epigenetics			X				X																									
Gene expression and proteomics			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	
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	
IXRSP	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug administration <sup>sc4</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subject training on self-injection <sup>r</sup>							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 5-2: 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	6H	8H	10H	12 wdt	14H	16H	18H	20H	22H	24 and Q12W wdt	52/WD <sup>a</sup>	FU <sup>a</sup>
Week Protocol Activity	0	2	4	12												
Vital signs <sup>b</sup>	X	X	X	X				X						X	X	X
Hematology/urine/biochemistry	X <sup>c,d</sup>			X				X						X	X <sup>d</sup>	X
CRP	X			X				X						X	X	X
Pregnancy testing <sup>e</sup>	X														X	X
PE <sup>f</sup>	X		X	X				X						X	X	X
Extra-articular assessments				X				X						X	X	
TB test <sup>h</sup>															X	
TB questionnaire	X							X						X	X	
BASMI & Spinal mobility <sup>i</sup>	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	

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<sup>e</sup>

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







**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		
<b>Week</b>	0	12	24 and Q12W		FU <sup>a</sup>
<b>Protocol Activity</b>					52/WD
Hematology/urine/biochemistry	X <sup>b,c</sup>				
CRP	X	X			X
Pregnancy testing <sup>e</sup>	X				X
PE	X				X
BASDAI	X	X			
BASFI	X	X			
Total and nocturnal spinal pain	X	X			
Swollen and tender joint counts					
Patient's Global assessment	X				
Investigator's AS assessment	X	X			
CZP plasma concentration/anti-CZP Abs/ Biomarker	X	X			X
Prior and Concomitant medication	X	X	X		X
AEs	X	X	X		X
IXRS <sup>e</sup>	X	X	X		X
Other treatment administration	X <sup>f</sup>	Follow the regimen of the particular alternative treatment. Telephone contact to be performed on the discretion of the Investigator			
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. <sup>d</sup>					

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

Week	Visit #	1 wdt	2 wdt	3 wdt	Continuation W24 assessment	FU <sup>a</sup>
Protocol Activity		0	12	24 and Q12W	52/WD	FU <sup>a</sup>

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.

<sup>a</sup> FU: 8 weeks after Week 52/WD visit.

<sup>b</sup> 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.  
<sup>c</sup> HbA1c will be measured at wdt Week 0.

<sup>d</sup> 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).

<sup>e</sup> For registration of visit only. Interactive Response System won't assign any open treatment medication.

<sup>f</sup> 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.

<sup>g</sup> 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 # <sup>a</sup>	1/ BL	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
<b>Week</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>4</b>	<b>6</b>	<b>8</b>	<b>10</b>	<b>12</b>	<b>14</b>	<b>16</b>	<b>18</b>	<b>20</b>	<b>22</b>	<b>24</b>	<b>26</b>	<b>28</b>	<b>30</b>	<b>32</b>	<b>34</b>	<b>36</b>	<b>38</b>	<b>40</b>	<b>42</b>	<b>44</b>	<b>46</b>	<b>48</b>	<b>50</b>
<b>Protocol Activity</b>																											
Vital signs									X	X	X	X	X	X	X	X	X	X	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	X	X
CRP					X		X		X	X	X	X	X	X	X	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	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	X	X	X
BASMI & spinal mobility					X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BASDAI					X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BASFI					X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36					X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ASQoL					X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MOS Sleep Scale					X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D					X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MASES					X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total and nocturnal spinal pain					X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
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	X	X
PhGADA					X		X		X	X	X	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	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 # <sup>a</sup>	1/ BL	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
<b>Week</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>4</b>	<b>6</b>	<b>8</b>	<b>10</b>	<b>12</b>	<b>14</b>	<b>16</b>	<b>18</b>	<b>20</b>	<b>22</b>	<b>24</b>	<b>26</b>	<b>28</b>	<b>30</b>	<b>32</b>	<b>34</b>	<b>36</b>	<b>38</b>	<b>40</b>	<b>42</b>	<b>44</b>	<b>46</b>	<b>48</b>	<b>50</b>
<b>Protocol Activity</b>																											
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	X	X	X
IXRS																											
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; BI=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

<sup>a</sup> 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 # <sup>a</sup>	1/ BL	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
<b>Week</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>4</b>	<b>6</b>	<b>8</b>	<b>10</b>	<b>12</b>	<b>14</b>	<b>16</b>	<b>18</b>	<b>20</b>	<b>22</b>	<b>24</b>	<b>26</b>	<b>28</b>	<b>30</b>	<b>32</b>	<b>34</b>	<b>36</b>	<b>38</b>	<b>40</b>	<b>42</b>	<b>44</b>	<b>46</b>	<b>48</b>	<b>50</b>
<b>Protocol Activity</b>																											
Hematology/urine/ biochemistry				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
BASDAI							X		X		X		X		X		X		X		X		X		X		X
BASFI							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
PhGADA							X		X		X		X		X		X		X		X		X		X		X
PGADA							X		X		X		X		X		X		X		X		X		X		X
IXRS							X		X		X		X		X		X		X		X		X		X		X

BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BL=Baseline; CRP=C reactive protein; 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=subcutaneous; wdt=withdrawal treatment

<sup>a</sup> Additional assessments to be performed correspond to the assessments to be performed at wdt Week 0.

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

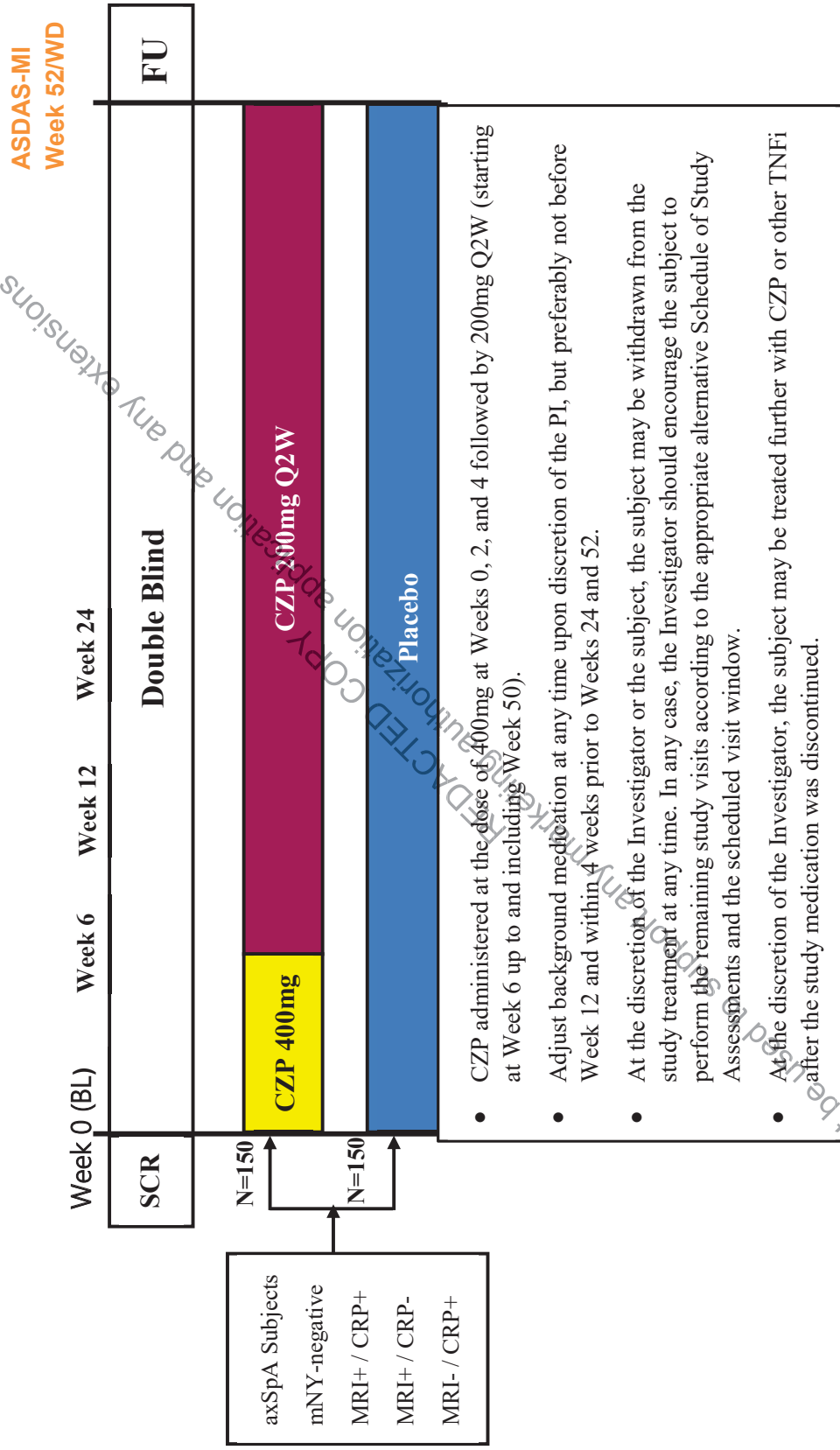
Visit #	29	30	31	32	33	34	35	36	37	38	39	40
Overall Study Week/SFE Week Protocol Activity	52/0 <sup>a</sup>	54/2	56/4	64/12	76/24	88/36	100/48	112/60	124/72	136/84	148/96	156/104/SFE-WD
Informed consent <sup>b</sup>	X											
CRP												X
BASDAI												X
BASFI												X
ASQoL												X
Total and nocturnal spinal pain												X
PGADA												X
MRI SI joints												X
AEs		X	X	X	X	X	X	X	X	X	X	X
IXRS <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Study drug loading dose administration <sup>sc,d</sup>	X	X	X									
Study drug dispensation <sup>e</sup>	X			X	X	X	X	X	X	X	X	X

AEs=adverse events; ASQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI= Bath Ankylosing Spondylitis Functional Index; CRP=C-reactive protein; CZP=Certolizumab pegol; FU=Follow-Up; IXRS=Interactive Response System; MRI=magnetic resonance imaging; PGADA=Patient's Global Assessment of Disease Activity; sc=subcutaneously; SFE=Safety Follow-Up Extension; SI=sacroiliac; WD=Withdrawal

- <sup>a</sup> 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.
- <sup>b</sup> A separate informed consent form will be obtained from subjects consenting to participate in the SFE Period.
- <sup>c</sup> 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.
- <sup>d</sup> 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).
- <sup>e</sup> 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**

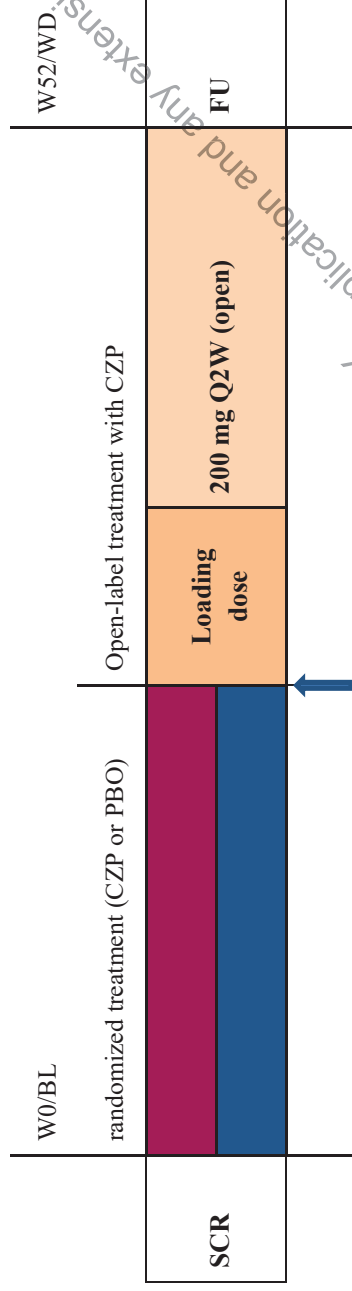


ASDAS-MI=Ankylosing Spondylitis Disease Activity Score major improvement; axSpA=axial spondyloarthritis; BL=Baseline; CRP=C-reactive protein; CZP=certolizumab pegol; FU=Follow-Up; mNY=modified New York criteria; MRI= magnetic resonance imaging; N=number of subjects; PI=Principal Investigator; Q2W=every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



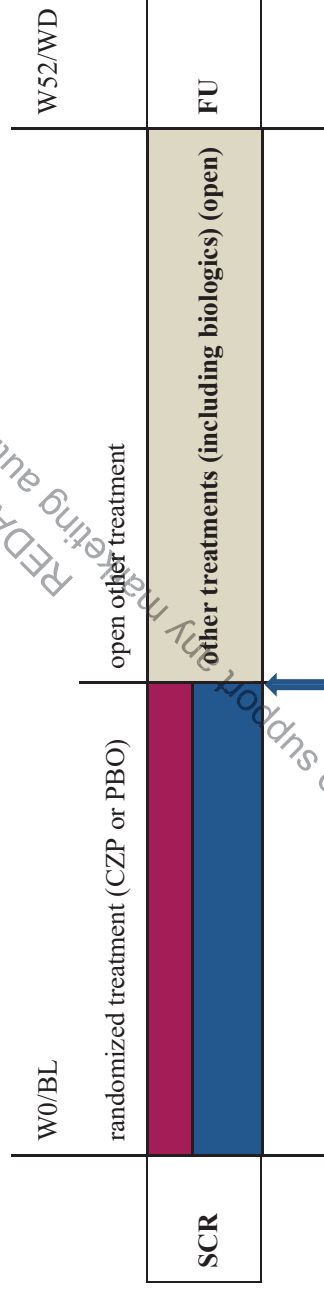
**Figure 5-2: Schematic diagram for subjects discontinued from the double-blind study treatment**

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



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

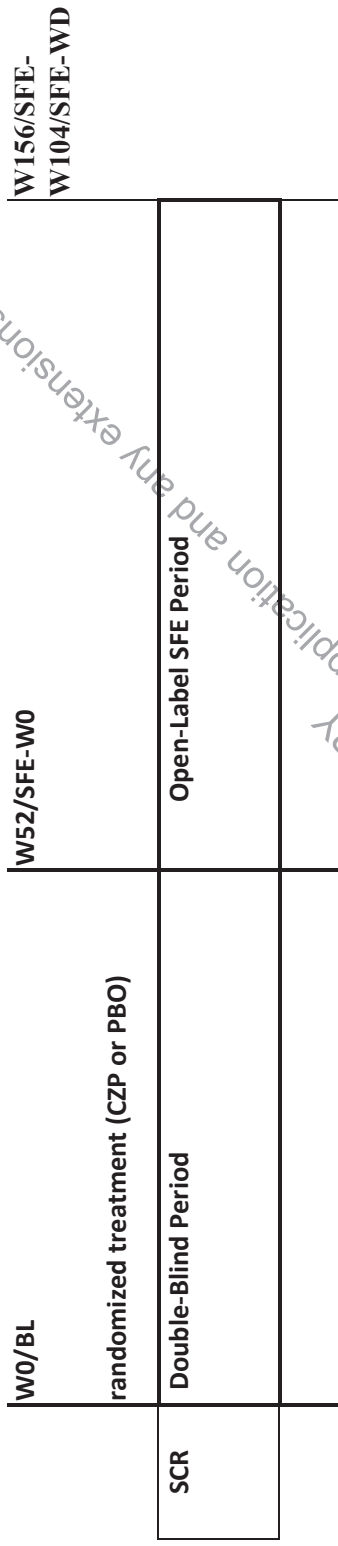
Scenario B: The subject initiates treatment with other treatments (including biologics)



At the discretion of the PI the double-blind 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; 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; WD=withdrawal

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 chooses 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 Appendix 18.2) (bilateral  $\geq$ Grade 2; unilateral  $\geq$ 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  $\geq$ 4
  - Spinal pain  $\geq$ 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  $\leq$ 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, Coccidioides, 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.

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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<sup>2</sup>
    - white blood cell ([WBC] <3.0x10<sup>9</sup>/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 case report form (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.

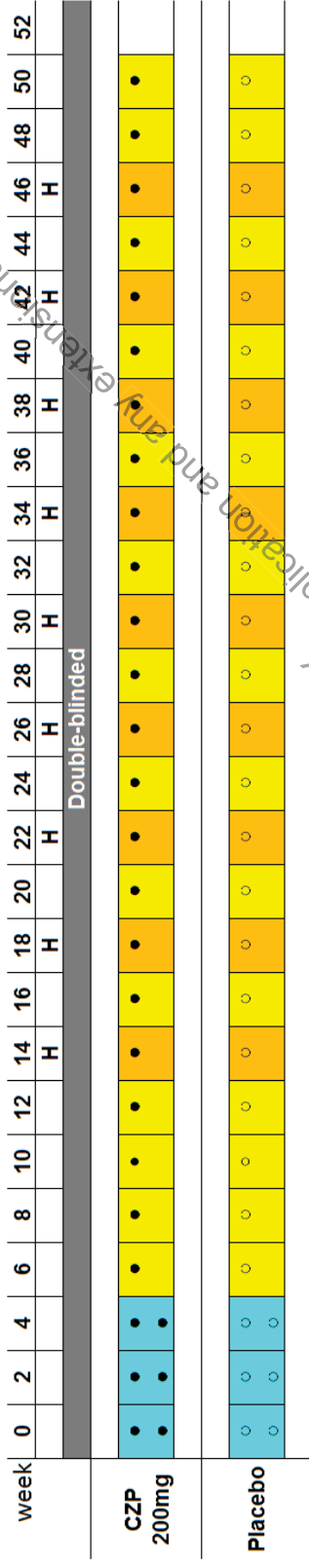
During the SFE Period, CZP will be administered sc by dedicated unblinded study personnel at the study site on Weeks 52, 54, and 56 for subjects completing double-blind treatment in order to maintain the blind. Subjects who complete the Week 52 Visit on placebo treatment will receive loading doses of 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**

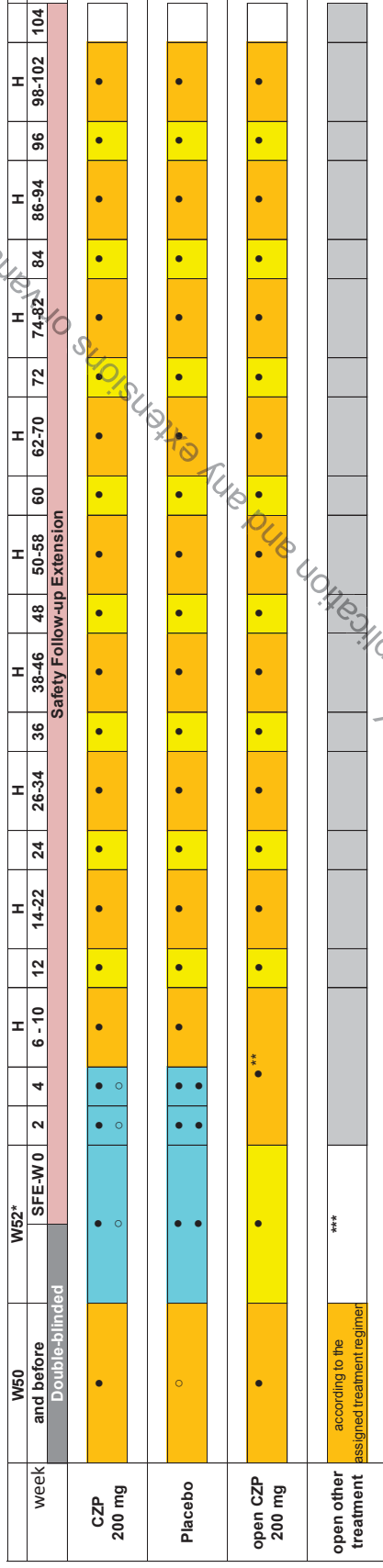


○ Placebo  
● CZP

**Loading doses**  
● On site (injection by unblinded site personnel)  
● Self-injection (by subject at home)  
 H Home

CZP=Certolizumab pegol; H=home

**Figure 7-2: Injection schedule for the SFE Period**



○ Placebo  
● CZP

□ Loading doses (on site, to be administered by unblinded site personnel only)  
□ On site (injection preferably by subject; or site personnel, if appr.)  
□ Self-injection (by subject at home)  
H Home

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.

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### **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 $\leq 10$ mg daily total prednisone equivalent <sup>a</sup>	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 $\leq 10$ mg daily total prednisone equivalent <sup>a</sup> 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 <sup>b</sup> : 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 <a href="#">Figure 5–2</a> .
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 <a href="#">Figure 5–2</a> .
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 <a href="#">Figure 5–2</a> . 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 bisphosphonates: 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

<sup>a</sup> A table of corticosteroid equivalent doses can be found in Appendix 18.3.

<sup>b</sup> 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  $\leq 10$ mg). Oral corticosteroid tapers of 14 days prior to Baseline are allowed as long as the maximum daily dose is  $\leq 10$ mg. 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 sacroiliac 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 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  $\pm 3$  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  $\pm 3$  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: Interferon-Gamma Release Assay (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  $\leq 12$  months prior to the Baseline visit may be 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  $\pm 3$  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)

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#### **8.4 Every 4 weeks ( $\pm$ 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 ( $\pm$ 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 ( $\pm 2$  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 the subject has withdrawn from the study, if applicable

At Week 156/SFE-WD ( $\pm 1$  week), all subjects are to visit the site for the following assessments:

- Blood sample for CRP
- BASDAI
- BASFI

- 
- ASQoL
  - Total and nocturnal spinal pain
  - PGADA
  - MRI SI joints
  - AEs
  - Contact IXRS to indicate that the subject has completed the SFE Period (Week 156/SFE WD)

### **8.7 FU visit (8 weeks after the Week 52/WD visit [ $\pm 3$ days])**

Subjects not participating in the SFE Period will attend a FU visit 8 weeks after the Week 52/WD visit ( $\pm 3$  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  $\pm 4$  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 chooses 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-Low Disease (ASDAS-LD): ASDAS  $\geq$ 1.3, <2.1
- ASDAS-High Disease Activity (ASDAS-HD): ASDAS  $\geq$ 2.1,  $\leq$ 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  $\geq$ 1.1 relative to Baseline
- ASDAS-Major Improvement (ASDAS-MI): ASDAS reduction (improvement) of  $\geq$ 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, 52/WD, and Week 156/SFE-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  $\leq 2$  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, 52/WD, and Week 156/SFE-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
  - $\geq 5$  days/week
  - Every day
- Starting date
- End date (or ongoing)

The general formula for calculation is as follows:

- (equivalent NSAID score)  $\times$  (days of intake during period of interest)  $\times$  (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)
  - $\geq 5$  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:

- $100 \text{ (20mg piroxicam score)} \times 120 \text{ (4 months)} \times 4/7 \text{ (3 to 5 days/week)} / 180 \text{ (6 months)} = 38.1$

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

- $50 \text{ (10mg piroxicam score)} \times 60 \text{ (2 months)} \times 2/7 \text{ (1 to 3 days/week)} / 180 \text{ (6 months)} = 4.8$

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, Table 5–2, and Table 5–6.

#### 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, Table 5–3, and Table 5–6.

#### **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, Table 5–3, and Table 5–6.

#### **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  $\geq 2$  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  $\geq 2$  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. A further MRI of the SI joints will be performed at Week 156/SFE-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, Table 5–3, and Table 5–6.

#### **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 [REDACTED]

[REDACTED] One of the WPS questions concerns the [REDACTED]. [REDACTED] will be asked questions about the [REDACTED]; [REDACTED] on a 0 to 10 scale (0=no interference; 10=complete interference). In addition, all subjects regardless of their employment status will be asked questions [REDACTED]

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

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

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### 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](#), [Table 5–3](#), and [Table 5–6](#).

## 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- $\beta$ , 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

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 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 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 LTB or active TB infection and risk factors for exposure to TB using the TB questionnaire.

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## **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.



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#### 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

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- 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.

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### 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  $\geq 3 \times \text{ULN}$  ALT or AST with coexisting  $\geq 2 \times \text{ULN}$  total bilirubin in the absence of  $\geq 2 \times \text{ULN}$  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

**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
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 <sup>a</sup>		
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		
	Bilirubin		
	Total cholesterol		
	HDL <sup>b</sup>		

**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
	LDL <sup>b</sup>		
	HbA1c <sup>c</sup>		
	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

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

<sup>b</sup> HDL and LDL are to be measured every 6 months and at the time the subject shifts to open-label CZP.

<sup>c</sup> 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. At Week 156/SFE-WD, a blood sample will be taken for CRP measurement and analyzed at the central laboratory.

## 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



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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 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).

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### 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 [REDACTED]” 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 “ [REDACTED] ” 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 AB). 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.

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### 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).

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## 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.

The SFE Full Analysis Set (SFE-FAS) will be defined as all subjects in the FAS 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. Analyses of efficacy variables in the SFE Period will be performed on the SFE-FAS.

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 or where requested by Regulatory Authorities):

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 ASDAS-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  $\geq 5$ , 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

<b>ASAS classification criteria for axial SpA</b>	
(for subjects with chronic back pain $\geq 3$ months and age at onset $< 45$ years)	
<b>Imaging criteria</b>	<b>ASAS clinical criteria for axial SpA</b>
Sacroiliitis (MRI or radiographs*) plus $\geq 1$ SpA feature	HLA-B27 plus $\geq 2$ other SpA features
<b>SpA features**</b>	
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

<b>Diagnosis</b>
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 $\geq 2$ bilaterally or sacroiliitis grade 3 to 4 unilaterally.
<b>Grading</b>
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).

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### 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)

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**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.  )

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Not active

very active

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### 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

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## 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 enters either 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:	208 Bath Road Slough Berkshire UK SL1 3WE
Phone:	[REDACTED]
Fax:	[REDACTED]



---

**Has been changed to:**

**Sponsor Study Physician**

Name:	██████████, MD
Address:	Alfred-Nobel-Str 10 40789 Monheim Germany
Phone:	██████████
Fax:	██████████

**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:**

TNF $\alpha$	tumor necrosis factor alpha
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**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 (Cuirena 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 (Cuirena 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 (TNF $\alpha$ ) 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

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## 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:

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## 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<sup>®</sup> TB test or Elispot<sup>®</sup> 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<sup>®</sup> TB test or Elispot<sup>®</sup> 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  $\geq 2$  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  $\pm 4$  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  $\geq 2$  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  $\pm 4$  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.

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## 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).

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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	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Week Protocol Activity	-6 weeks to -1 day		0	1	2	4	6	8	10	11	12	14	16	18	20	22	24	26	30	32	34	36	38	40	42	44	46	48	50	52	FU
IXRS	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X

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## 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.

- <sup>a</sup> 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.
- <sup>d</sup> 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.
- <sup>f</sup> 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.
- <sup>g</sup> 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.
- <sup>k</sup> 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.
- <sup>n</sup> 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 ~~se~~ 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.
- <sup>o</sup> 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:

- <sup>a</sup> 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.
- <sup>d</sup> 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.
- <sup>e</sup> HbA1c will be measured at Baseline and Week 52/WD.

- 
- <sup>f</sup> 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.
- <sup>h</sup> 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.
- <sup>i</sup> 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.
- <sup>m</sup> 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.
- <sup>p</sup> Contact IXRS to register the visit and obtain next kit number, where applicable.
- <sup>q</sup> 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.
- <sup>r</sup> 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	3	5	6								
Week Protocol Activity	0	2	4	10	12	14 H	16H	18 H	20 H	22 H	24 and Q12W		FU <sup>a</sup>
Telephone contact <sup>k</sup>							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	2	3	5	6								
Week Protocol Activity	0	2	4	10	12	14 H	16H	18 H	20 H	22 H	24 and Q12W		FU <sup>a</sup>

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	2	3	4	5								
Week Protocol Activity	0	2	4	10	12	14 H	16H	18 H	20 H	22 H	24 and Q12W		FU <sup>a</sup>







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### 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  $\pm 3$  days compared to Baseline. Week 0 of the alternative schedule starts 2 weeks after the last dose of the study treatment.

- <sup>d</sup> 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.
- <sup>e</sup> If the last Q12W assessment for a subject who discontinues study treatment is  $\leq 4$  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 ( $\pm 3$  days) after Baseline).

#### Have been changed to:

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

- <sup>c</sup> 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.
- <sup>d</sup> HbA1c will be measured at wdt Week 0 and Week 52/WD.
- <sup>f</sup> 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.
- <sup>g</sup> If the last Q12W assessment for a subject who discontinues study treatment is  $\leq 4$  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 [ $\pm 3$  days] after Baseline).
- <sup>k</sup> 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).
- <sup>m</sup> 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	2	3	
Week	0	12	24 and Q12W	52/WD
Protocol Activity				FU <sup>a</sup>
Other treatment administration		Follow the regimen of the particular alternative treatment.		
				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.

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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	2	3			
Week	0	12	24 and Q12W		S2/WVD	FU <sup>a</sup>
Protocol Activity						
Other treatment administration		Follow the regimen of the particular alternative treatment. Telephone contact to be performed on the discretion of the investigator		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.		

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## 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  $\pm 3$  days compared to Baseline. Week 0 of the alternative schedule starts 2 weeks after the last dose of the study treatment.

- <sup>b</sup> If the last Q12W assessment for a subject who discontinues study treatment is  $\leq 4$  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 [ $\pm 3$  days] after Baseline).

#### Have been changed to:

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

- <sup>b</sup> 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.
- <sup>c</sup> HbA1c will be measured at wdt Week 0.
- <sup>d</sup> If the last Q12W assessment for a subject who discontinues study treatment is  $\leq 4$  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 [ $\pm 3$  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

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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.

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**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 # <sup>a</sup>	1/ BL	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Week	0	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Protocol Activity									/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H
Vital signs									X	X	X	X	X	X	X	X	X	X	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	X	X
CRP					X		X		X	X	X	X	X	X	X	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	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	X
BASMI & spinal mobility					X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BASDAI					X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BASFI					X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36					X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ASQoL					X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MOS Sleep Scale					X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D					X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MASES					X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total and nocturnal spinal pain					X		X		X	X	X	X	X	X	X	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 # <sup>a</sup>	1/ BL	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
<b>Week</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>4</b>	<b>6</b>	<b>8</b>	<b>10</b>	<b>12</b>	<b>14</b>	<b>16</b>	<b>18</b>	<b>20</b>	<b>22</b>	<b>24</b>	<b>26</b>	<b>28</b>	<b>30</b>	<b>32</b>	<b>34</b>	<b>36</b>	<b>38</b>	<b>40</b>	<b>42</b>	<b>44</b>	<b>46</b>	<b>48</b>	<b>50</b>
<b>Protocol Activity</b>									/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H	/H
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	X	X	X	X
PhGADA				X	X	X	X	X	X	X	X	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	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	X	X	X	X
IXRS									X	X	X	X	X	X	X	X	X	X	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=subcutaneous; 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 # <sup>a</sup>	1/ BL	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
<b>Week</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>4</b>	<b>6</b>	<b>8</b>	<b>10</b>	<b>12</b>	<b>14</b>	<b>16</b>	<b>18</b>	<b>20</b>	<b>22</b>	<b>24</b>	<b>26</b>	<b>28</b>	<b>30</b>	<b>32</b>	<b>34</b>	<b>36</b>	<b>38</b>	<b>40</b>	<b>42</b>	<b>44</b>	<b>46</b>	<b>48</b>	<b>50</b>
<b>Protocol Activity</b>																											
Hematology/urine/ biochemistry				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
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	
IXRS									X		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

<sup>a</sup> Additional assessments to be performed correspond to the assessments to be performed at wdt Week 0.

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**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 Exclusion criteria, exclusion criterion 29, first subcriterion**

29. Subjects with significant laboratory abnormalities, including but not limited to:

- liver function tests  $>2.0 \times \text{ULN}$ , if the subject is not treated with MTX and  $>\text{ULN}$  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  $>2.0 \times \text{ULN}$

**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 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) from other sources in compliance with local regulations. All results of observations and communication with the subject, including and

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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 <sup>b</sup> : 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 <a href="#">Figure 5–2</a> .

**Has been changed to:**

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

Drug class	Dose	Exclusion criteria	Study Visits
SAARDs <sup>b</sup> : 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 <a href="#">Figure 5–2</a> .

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## 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 $\pm 3$ 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 ( $\pm 3$ days)**

##### **8.5 Completion Visit (Week 52)/Early Withdrawal ( $\pm 3$ days)**

#### **Has been changed to:**

##### **8.5 Week 52/WD ( $\pm 3$ days)**



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### **Change #40**

#### **Section 8.5 Completion Visit (Week 52)/Early Withdrawal ( $\pm 3$ 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 [ $\pm 3$ 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  $\pm 3$  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)

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**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)
  - $\geq 5$  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)
  - $\geq 5$  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**

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**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](#).

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### **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 (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 two consecutive slices (Rudwaleit et al, 2009d). In practice this is very similar to the SPARCC SIJ  $\geq 2$  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  $\geq 2$  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.

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**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  $\geq 2$  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  $\geq 2$  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](#).

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**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](#).

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**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**

**Apolipoproteins and lipoprotein(a) have been added to Table 12-1 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).



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## 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 “ [REDACTED] ” 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 “ [REDACTED] ” 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 “ [REDACTED] ” 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 [REDACTED] 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

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### **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

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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.



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## 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

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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.

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## Change #80

### Section 17 References

Callhoff J, Sieper J, Weiß A, Zink A, Listing J. Efficacy of TNF $\alpha$  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 TNF $\alpha$  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 Rheum*. 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 Rheum*. 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,

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**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”**

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## 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:	██████████, MS
Address:	8010 Arco Corporate Drive Raleigh, NC 27617 United States
Phone:	██████████
Fax:	██████████

Has been changed to:

##### Clinical Trial Biostatistician

Name:	██████████, MS
Address:	8010 Arco Corporate Drive Raleigh, NC 27617 United States of America
Phone:	██████████
Fax:	██████████



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## Change #2

### Section 1 Summary, paragraph 2

The study population will be subjects ( $\geq 18$  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)  $\geq 4$ , and spinal pain  $\geq 4$  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 ( $\geq 18$  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)  $\geq 4$ , and spinal pain  $\geq 4$  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.

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#### **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<sup>®</sup> TB test or Elispot<sup>®</sup> 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<sup>®</sup> TB test or Elispot<sup>®</sup> 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**

<sup>j</sup> 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:**

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).

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## Change #9

### Section 5.2 Schedule of study assessments - Study Periods 1 to 3 (Screening until FU), Table 5-1: footnote q

<sup>q</sup> 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:

<sup>q</sup> 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

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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.

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## 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  $\geq 3 \times \text{ULN}$  ALT or AST with coexisting  $\geq 2 \times \text{ULN}$  total bilirubin in the absence of  $\geq 2 \times \text{ULN}$  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.**

<b>Serious Adverse Event reporting (24h) and safety related issues</b>	
<b>Fax</b>	<b>Europe and Rest of the World:</b> +32 2 386 24 21 <b>USA and Canada:</b> +1 800 880 6949 or +1 866 890 3175
<b>E-Mail</b>	<b>DS_ICT@ucb.com</b>

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### 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.



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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,

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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 3<sup>rd</sup> 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.

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## 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/SFE-WD.

### **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

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## 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](#):

<sup>b</sup> FU: 8 weeks after Week 52/WD visit.

---

**Has been changed to:**

<sup>b</sup> FU: 8 weeks after Week 52/WD visit for subjects not participating in the SFE.

**And footnote k under Table 5-1:**

<sup>k</sup> 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:**

<sup>k</sup> 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:**

<sup>a</sup> FU: 8 weeks after Week 52/WD visit.

**Has been changed to:**

<sup>a</sup> 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:**

<sup>g</sup> 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 <sup>a</sup>	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 <sup>b</sup>	X											
AEs		X	X	X	X	X	X	X	X	X	X	X
IXRS <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Study drug loading dose administration <sup>scd</sup>	X	X	X									
Study drug dispensation <sup>e</sup>	X			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;

<sup>a</sup> 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.

<sup>b</sup> A separate informed consent form will be obtained from subjects consenting to participate in the SFE Period.

<sup>c</sup> 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.

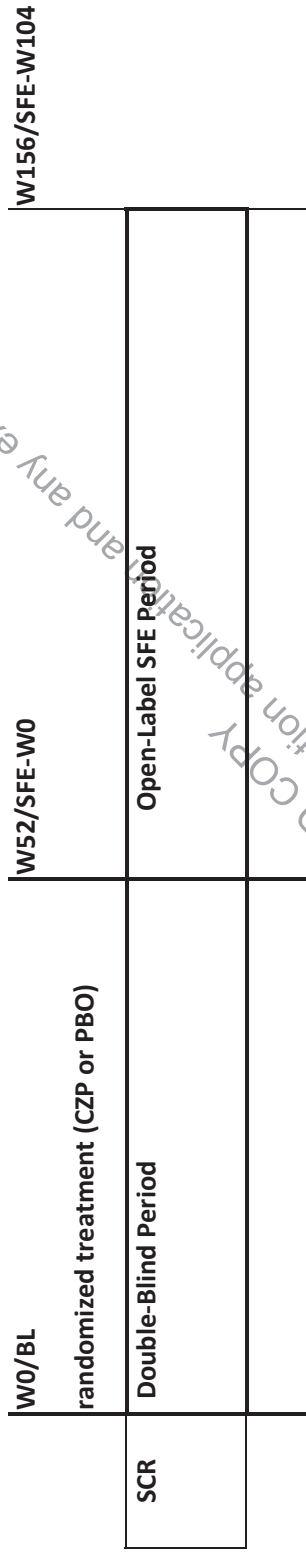
<sup>d</sup> At Weeks 52, 54, and 56, study treatment administration should be performed at the site by unblinded study personnel in order to keep the blind (see Section 7.2.1).

<sup>e</sup> 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).



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## 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.

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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:**

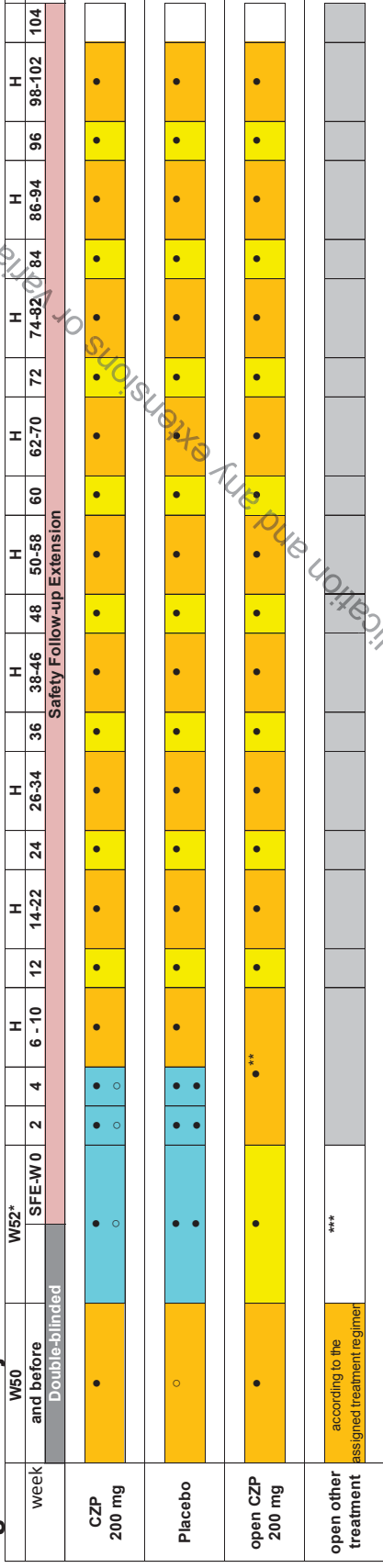
**Figure 7-1: Injection schedule**

##### **Has been changed to:**

**Figure 7-1: Injection schedule through Week 52**

Change #20 An injection schedule for the OLE Period (Figure 7-2) has been added:

**Figure 7-2: Injection schedule for the SFE Period**



○ Placebo  
● CZP

● Loading doses (on site, to be administered by unblinded site personnel only)  
○ On site (injection preferably by subject; or site personnel, if appr.)  
● Self-injection (by subject at home)  
H Home

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.

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## **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  $\pm 3$  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  $\pm 3$  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  $\pm 3$  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  $\pm 3$  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.

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### **Change #28**

#### **Section 8.5 Week 52/WD ( $\pm 3$ 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 (Week 156/WD)

### **Change #30**

#### **Section 8.6 FU visit (8 weeks after the Week 52/WD visit ( $\pm 3$ 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 ( $\pm 3$  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  $\geq 3 \times \text{ULN}$  ALT or AST with coexisting  $\geq 2 \times \text{ULN}$  total bilirubin in the absence of  $\geq 2 \times \text{ULN}$  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).



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**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).

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**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.

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### **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.

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**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).

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## 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.

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## 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)

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**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

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- 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.



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**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- $\beta$ , 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- $\beta$ , 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.

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## 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

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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  $\geq 5$ , 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 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.

#### **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)

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## 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



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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.

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**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.

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## 18.17 Protocol Amendment 5

### Rationale for the amendment

The purpose of this substantial amendment is to gain additional information about the longer-term disease progress and the effects of CZP treatment in patients with nr-axSpA. To support this, several PROs, a lab assessment, and an additional SI joint MRI will be taken at Week 156/SFE-WD as updated in Table 5–6. The visit windows for the SFE Period were also clarified.

Additional changes include:

- An update to other efficacy variables to include the Week 156/SFE-WD timepoint. SFE-WD added to Week 156 instances when needed to distinguish from Week 52/WD.
- An update to Table 5–5 to remove collection of samples for CZP plasma concentration, anti-CZP antibodies, and Biomarkers as this is not done for subjects on alternative treatments.
- An update to the subheadings in Section 4.2.2, Section 4.2.3, and Section 4.3 to clarify categorization of variables.
- An update to Section 4.4 subheadings to clarify safety variables.
- An update of ASDAS-MD to ASDAS-LD (Machado et al, 2018).
- Minor editorial and administrative changes have been made throughout the protocol.

### Modifications and changes

#### Specific changes

#### Change #1

#### Study Contact Information

#### Clinical Trial Biostatistician

Name:	[REDACTED], MS
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Phone:	[REDACTED]
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#### Has been changed to:

#### Clinical Trial Biostatistician

Name:	[REDACTED], PhD
Address:	Alfred-Nobel-Str 10 40789 Monheim

	Germany
Phone:	
Fax:	

## Change #2

### List of abbreviations

The following terms were added or modified:

ASDAS-LD	Ankylosing Spondylitis Disease Activity Score low disease
TEAE	treatment-emergent adverse event
SFE-FAS	Safety Follow-Up Full Analysis Set

## Change #3

### Section 2.5 Rationale

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.

#### Has been changed to:

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. In addition, MRI assessment of SI joint structural damage and laboratory assessment for CRP will be performed, and data from other selected efficacy variables will be collected at the end of the SFE Period. 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 #4

### Section 4.1.3 Other efficacy variables

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

#### Has been changed to:

The following variables will be analyzed at scheduled time points through Week 52 and at Week 156 for selected variables:

## Change #5

### Section 4.1.3 Other efficacy variables, bullets 5, 6, 10, and 11

- 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)
- 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

**Has been changed to:**

- Change from Baseline in BASMI linear
- ASDAS disease activity (Ankylosing Spondylitis Disease Activity Score inactive disease [ASDAS-ID], Ankylosing Spondylitis Disease Activity Score low disease [ASDAS-LD; Machado et al, 2018], 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)
- Change from Baseline in SI joint SPARCC score at Week 52 and Week 156 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, Week 52, and Week 156

**Change #6**

**The following text was moved from Section 4.4 Safety variables to Section 12 Assessment of Safety:**

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<sup>®</sup>) criteria.

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 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

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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 IGRA test (QuantiFERON<sup>®</sup> TB test or Elispot<sup>®</sup> 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 LTB or active TB infection and risk factors for exposure to TB using the TB questionnaire.

#### **Change #7**

**The following section was added:**

##### **Section 4.4.1 Secondary safety variables**

Assessment time points for safety variables are specified in [Table 5–1](#) and [Table 5–6](#). The secondary safety variables are as follows:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of serious adverse events (SAEs)
- Adverse events leading to withdrawal from investigational medicinal product (IMP)

#### **Change #8**

**The following section was added:**

##### **Section 4.4.2 Other safety variables**

Other safety variables are assessed as specified in [Table 5–1](#) and [Table 5–6](#), and are as follows:

- Change from Baseline in vital signs (blood pressure, temperature, and pulse rate)
- Change from Baseline in clinical laboratory values (hematology, biochemistry, and urinalysis)

Physical examination findings considered clinically significant changes since the physical examination completed at the Screening Visit will be recorded as AEs.

#### **Change #9**

##### **Section 5.1.1 Study periods**

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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.

**Has been changed to:**

Starting at Week 64, all subjects are to visit the site approximately every 12 weeks ( $\pm 2$  weeks) for-assessments.

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

**Change #10**

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

The CZP-plasma concentration/anti-CZP Abs/Biomarker row was removed. The table list of abbreviations was updated.

**Change #11**

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

At Week 156 (Visit 40), the following assessments were added: blood sample for CRP, BASDAI, BASFI, ASQoL, total and nocturnal spinal pain, PGADA, and MRI SI joints. The table list of abbreviations was updated.

The column header for Visit 40 was updated to 156/104/SFE-WD. The table list of abbreviations was updated.

**Change #12**

**Figure 5–3: Schematic diagram for subjects completing the double-blind study treatment and rolling over to the SFE Period**

The label for Week 156 was updated to W156/SFE-W104/SFE-WD. The schematic list of abbreviations was also updated.

**Change #13**

**Section 8.6 SFE Period (Week 52 to Week 156):**

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)

**Has been changed to:**

Starting at Week 64, all subjects are to visit the site approximately every 12 weeks ( $\pm 2$  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 the subject has withdrawn from the study, if applicable

At Week 156/SFE-WD ( $\pm 1$  week), all subjects are to visit the site for the following assessments:

- Blood sample for CRP
- BASDAI
- BASFI
- ASQoL
- Total and nocturnal spinal pain
- PGADA
- MRI SI joints
- AEs
- Contact IXRS to indicate that the subject has completed the SFE Period (Week 156/SFE-WD)

**Change #14**

**Section 9.1.1 ASDAS**

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  $\geq 1.3$ ,  $< 2.1$
  - ASDAS-High Disease Activity (ASDAS-HD): ASDAS  $\geq 2.1$ ,  $\leq 3.5$
  - ASDAS-very High Disease Activity (ASDAS-vHD): ASDAS  $> 3.5$

**Has been changed to:**

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

- ASDAS-Inactive Disease (ASDAS-ID): ASDAS  $< 1.3$
- ASDAS-Low Disease (ASDAS-LD): ASDAS  $\geq 1.3$ ,  $< 2.1$
- ASDAS-High Disease Activity (ASDAS-HD): ASDAS  $\geq 2.1$ ,  $\leq 3.5$
- ASDAS-very High Disease Activity (ASDAS-vHD): ASDAS  $> 3.5$

**Change #15**

**Section 9.1.1 ASDAS**

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.

**Has been changed to:**

The ASDAS will be calculated at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52/WD, and Week 156/SFE-WD.

**Change #16**

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

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.

**Has been changed to:**

The ASDAS will be calculated at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52/WD, and Week 156/SFE-WD.

**Change #17**

**Section 9.1.4 ASQoL**

The ASQoL assessments per visit are described in [Table 5–1](#) and [Table 5–2](#).

**Has been changed to:**

The ASQoL assessments per visit are described in [Table 5–1](#), [Table 5–2](#), and [Table 5–6](#).

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## **Change #18**

### **Section 9.1.5 BASDAI**

The BASDAI assessments per visit are described in the schedule of study assessments [Table 5-1](#), [Table 5-2](#), and [Table 5-3](#).

#### **Has been changed to:**

The BASDAI assessments per visit are described in the schedule of study assessments [Table 5-1](#), [Table 5-2](#), [Table 5-3](#), and [Table 5-6](#).

## **Change #19**

### **Section 9.1.6 BASFI**

The BASFI assessments per visit are described in [Table 5-1](#), [Table 5-2](#), and [Table 5-3](#).

#### **Has been changed to:**

The BASFI assessments per visit are described in [Table 5-1](#), [Table 5-2](#), [Table 5-3](#), and [Table 5-6](#).

## **Change #20**

### **Section 9.1.12 MRI assessments**

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.

#### **Has been changed to:**

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. A further MRI of the SI joints will be performed at Week 156/SFE-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 #21**

### **Section 9.1.13 PGADA (NRS)**

The PGADA assessments per visit are described in [Table 5-1](#), [Table 5-2](#), and [Table 5-3](#).

#### **Has been changed to:**

The PGADA assessments per visit are described in [Table 5-1](#), [Table 5-2](#), [Table 5-3](#), and [Table 5-6](#).

## **Change #22**

### **Section 9.1.20 Total and nocturnal spinal pain NRS**

The pain NRS assessments per visit are described in Table 5–1, Table 5–2, and Table 5–3.

#### **Has been changed to:**

The pain NRS assessments per visit are described in Table 5–1, Table 5–2, Table 5–3, and Table 5–6.

## **Change #23**

### **Section 12.5 Laboratory measurements**

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.

#### **Has been changed to:**

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. At Week 156/SFE-WD, a blood sample will be taken for CRP measurement and analyzed at the central laboratory.

## **Change #24**

### **Section 14.1 Definition of analysis sets**

The following analysis set was added:

The SFE Full Analysis Set (SFE-FAS) will be defined as all subjects in the FAS, who continued into the SFE Period and who received at least 1 dose of CZP in the SFE Period.

## **Change #25**

### **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.

#### **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. Analysis of efficacy variables in the SFE Period will be performed on the SFE-FAS.

## **Change #26**

### **Section 17 References**

#### **The following reference was added:**

Machado PM, Landewé R, van der Heijde D, Assessment of SpondyloArthritis international Society (ASAS). Letter. Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. Ann Rheum Dis. 2018;77:1539-40.

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## 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:

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Printed name

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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.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.

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## Approval Signatures

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### Document Approvals

Approval Verdict: Approved	Name: [REDACTED] Capacity: Clinical Date of Signature: 18-Dec-2018 14:18:05 GMT+0000
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Approval Verdict: Approved	Name: [REDACTED] Capacity: Clinical Date of Signature: 18-Dec-2018 16:02:22 GMT+0000

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