PROTOCOL AS0005 AMENDMENT 2

MULTICENTER, OPEN-LABEL (PART A) FOLLOWED BY A RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED STUDY (PART B) TO EVALUATE MAINTENANCE OF REMISSION IN SUBJECTS WITH ACTIVE AXIAL SPONDYLOARTHRITIS (AXSPA) RECEIVING EITHER CERTOLIZUMAB PEGOL 200MG Q2W OR 200MG Q4W AS COMPARED TO PLACEBO

PHASE 3B

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Confidential Material

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
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AB	antibody
ABA	abatacept
ADA	adalimumab
ADAb	anti-CZP antibody
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASAS20, 40	Assessment of SpondyloArthritis International Society 20%, 40% response criteria
ASAS5/6	ASAS 5 out of 6 response criteria
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASDAS-CII	Ankylosing Spondylitis Disease Activity Score – Clinically Important Improvement
ASDAS-HD	Ankylosing Spondylitis Disease Activity Score – High Disease activity
ASDAS-ID	Ankylosing Spondylitis Disease Activity Score – Inactive Disease
ASDS-MD	Ankylosing Spondylitis Disease Activity Score – Moderate Disease
ASDAS-MI	Ankylosing Spondylitis Disease Activity Score – Major Improvement
ASDAS-vHD	Ankylosing Spondylitis Disease Activity Score – very High Disease activity
ASQoL	Ankylosing Spondylitis Quality of Life
ASspIMRI-a	Ankylosing Spondylitis spine MRI score for activity
axSpA	axial spondyloarthritis
AZA	azathioprine
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 morphogenic protein
CD	Crohn's disease
CDMS	clinical data monitoring system
CI	confidence interval
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
CZP	certolizumab pegol
DKK1	Dickkopf-related protein 1
DMARD	disease-modifying antirheumatic drug
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
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
FDS	Full Dose Set
FS	Flared Set
GCP	Good Clinical Practice
GM-CSF	Granulocyte macrophage colony-stimulating factor
GOL	golimumab
HCQ	hydroxychloroquine
HIV	human immunodeficiency virus
HLA-B27	human leukocyte antigen B27
HRQoL	health-related quality of life
ia	intra-articular
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBD-Q	inflammatory bowel disease questionnaire
IBP	inflammatory back pain
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFX	infliximab
IGRA	interferon-gamma release assay
IMP	investigational medicinal product

IP	interphalangeal
IRB	Institutional Review Board
iv	intravenous
IXRS	interactive voice or web response system (IVRS or IWRS)
LFN	leflunomide
LOCF	last observation carried forward
LTB	latent tuberculosis
M-CSF	macrophage colony-stimulating factors
MASES	Maastricht Ankylosis Spondylitis Enthesitis Score
MCID	minimal clinically important difference
MCS	Mental Component Summary
MMP-3	matrix metalloproteinase-3
MMRM	mixed model for repeated measures
mNY	modified New York
MRI	magnetic resonance imaging
MTX	methotrexate
NAb	neutralizing antibody
nr-axSpA	nonradiographic axSpA
NRI	nonresponse imputation
NRS	Numeric Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
NTMB	nontuberculosis mycobacterium
NYHA	New York Heart Association
OLS	Open-Label Set
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PCS	Physical Component Summary
PEG	polyethylene glycol
PFS	prefilled syringe
PhGADA	Physician's Global Assessment of Disease Activity
PtGADA	Patient's Global Assessment of Disease Activity
PK	pharmacokinetics
PKSA	Pharmacokinetic Set A
PKSB	Pharmacokinetic Set B
PPS	Per Protocol Set

PR	partial remission
prn	pro re nata (as needed)
PS	Patient Safety
PsA	psoriatic arthritis
Q2W	every 2 weeks (every other week)
Q4W	every 4 weeks
QoL	quality of life
RA	rheumatoid arthritis
RDC	remote data capture
RS	Randomized Set
SAARD	slow-acting anti-rheumatic drugs
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
sCSF1r	soluble CSF-1 Receptor
SD	standard deviation
SF-36	Short-Form 36-Item Health Survey
SFU	Safety Follow-Up
SI	sacroiliac
SIJ	sacroiliac joint
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SS	Safety Set
SSB	Safety Set Part B
SSCM	Single Safety Case Management
SSZ	sulfasalazine
STIR	short-tau-inversion recovery
TB	tuberculosis
TGF	Transforming Growth Factor
TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal

VAS	visual analog scale
VEGF	vascular endothelial growth factor
WBC	white blood cell
WD	Withdrawal
WHO	World Health Organization
WISP	Inducible Signaling Pathway proteins
WNT-1	wingless-related mouse mammary tumor virus integration site protein
WPS	Work Productivity Survey

1 SUMMARY

Study AS0005 is a multicenter, open-label (Part A) followed by a randomized, double-blind, parallel-group, placebo-controlled clinical study (Part B) to evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of certolizumab pegol (CZP) in adult subjects with active axial spondyloarthritis (axSpA) in sustained remission who continued either on full-dose treatment (CZP 200mg every 2 weeks [Q2W]), on a dose reduction (CZP 200mg every 4 weeks [Q4W]) or withdrawal of CZP treatment (placebo). The study includes an Open-Label Run-In Period of 48 weeks (Part A) followed by a Double-Blind Period of 48 weeks (Part B) with 3 treatment arms (200mg CZP Q2W [referred to as full-dose], 200mg CZP Q4W [referred to as half-dose], and placebo), and a Safety Follow-Up (SFU) Period for 10 weeks after the last dose of study medication.

Part A consists of 2 periods: Period 1 (Screening Period), 1 to 5 weeks before Baseline and Period 2 (Open-Label Period), Week 0 (Baseline) to Week 48. Eligible subjects will receive 3 loading doses of CZP 400mg subcutaneous (sc) at Weeks 0 (Baseline), 2, and 4 followed by CZP 200mg Q2W in Period 2 from Week 6 to Week 46. All subjects who have not achieved sustained remission at the end of Period 2 will be discontinued from the study and treated at the discretion of their physician.

Part B consists of 2 periods: Period 3 (Double-Blind Period): Week 48 to Week 96, placebo-controlled and Period 4 (SFU Period): 10 weeks after the last dose of study medication. Subjects in sustained remission at the end of Part A will be randomized in a 1:1:1 ratio to the following treatment arms: 1) CZP administered sc at a dose of 200mg Q2W (full-dose), 2) CZP administered sc at a dose of 200mg Q4W (half-dose), and 3) placebo. All subjects, including those withdrawn from study treatment, will have an SFU Visit, 10 weeks after their last dose of study medication. Subjects experiencing a flare after randomization will be further treated with CZP 200mg Q2W (full-dose) until Week 96 or for at least 12 weeks after the flare, whatever period is longer (refer to Figure 7.1).

The primary objective of the study is to evaluate the percentage of subjects who do not experience a flare on CZP 200mg Q2W (full-dose) or 200mg Q4W (half-dose) during Part B. The secondary objectives are as follows: 1) to evaluate the percentage of subjects achieving sustained remission at the end of Part A, 2) to evaluate the time to flare and other measures of signs and symptoms, to compare the percentage of subjects who do not experience a flare between CZP full-dose and half-dose, and to evaluate the efficacy of re-initiation of treatment with the CZP full-dose in subjects who experience a flare following a withdrawal or dose reduction of CZP for subjects randomized into Part B, 3) to assess safety and tolerability of CZP, and 4) to evaluate inflammatory changes over time as assessed by magnetic resonance imaging (MRI).

The other objectives as well as pharmacokinetic, pharmacogenomic, and immunological objectives are presented in Sections 3.3 and 3.4.

The primary efficacy variable is the percentage of subjects in Part B who do not experience a flare (refer to Section 3 for definition of flare). Secondary efficacy variables for subjects entering Part A are: 1) percentage of subjects achieving sustained remission at Week 48 and 2) Ankylosing Spondylitis Disease Activity Score (ASDAS) disease activity and clinical improvement at Week 48.

The following are secondary efficacy variables for subjects entering Part B: 1) time to flare, 2) ASDAS disease activity and clinical improvement at Week 96, 3) assessment in Axial SpondyloArthritis International Society (ASAS) response criteria (ASAS20, ASAS40, ASAS 5 out of 6 [ASAS 5/6], and ASAS partial remission [PR] responses) at Week 96, 4) change from Baseline in ASDAS, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 96, 5) BASDAI50 response at Week 96, and 6) change from Baseline in Sacroiliac SpondyloArthritis Research Consortium of Canada (SPARCC) and ankylosing spondylitis spine MRI score for activity (ASspIMRI-a) in the Berlin modification scores at Week 96.

The following are secondary efficacy variables for subjects who experience a flare in Part B. These will be evaluated at Escape Week 12: 1) ASDAS disease activity and clinical improvement, 2) ASAS20, ASAS40, ASAS5/6, and ASAS PR response, 3) change from Baseline in ASDAS, BASDAI, BASFI, BASMI, and 4) change from Baseline in sacroiliac SPARCC and ASspIMRI-a in the Berlin modification scores.

Further, other efficacy variables for Part A, Part B and for subjects who experience a flare in Part B are listed in Section 4.1.3.1, Section 4.1.3.2, and Section 4.1.3.3, respectively.

Pharmacokinetic and pharmacogenomic variables are listed in Section 4.2, and immunological variables are listed in Section 4.3.

Safety variables to be assessed are adverse events (AEs), physical examination, blood pressure, chest x-ray, and measurements of laboratory parameters (hematology, biochemistry, and urinalysis). At Screening, Week 48, and Week 96, all subjects will have an interferon-gamma release assay (IGRA) test (QuantiFERON TB GOLD In Tube test or another World Health Organization (WHO)-validated IGRA test such as Elispot, if QuantiFERON TB GOLD In Tube test is not available locally). Screening chest x-ray must have occurred within 3 months prior to Screening Visit and should be repeated only if the tuberculosis (TB) test was confirmed positive or any further evidence is suggestive of potential TB infection. In addition to a physical examination done intermittently throughout the study, subjects will be evaluated at Screening, Baseline, and every 12 weeks thereafter, including the Week 96/Withdrawal (WD) Visit, for signs and symptoms of latent or active TB infection and risk factors for exposure to TB using the TB questionnaire.

Additionally it is planned to evaluate whether the response of axSpA-associated gut inflammation to CZP correlates with the response of the axSpA signs and symptoms. Correlation of fecal and serum calprotectin level with Inflammatory Bowel Disease Questionnaire (IBD-Q) and C-reactive protein (CRP) level will be evaluated in an exploratory manner.

2 INTRODUCTION

2.1 Natural history of axial spondyloarthritis

Spondyloarthritis (SpA) is an umbrella term applied to a family of rheumatic diseases that have both features in common with, as well as being 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 SpA and axSpA (Rudwaleit, 2011; Rudwaleit, 2010; Rudwaleit,

2009c). 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 (sacroiliac joints and spine), including ankylosing spondylitis (AS) and nonradiographic axSpA (nr-axSpA).

Patients with AS have definitive evidence of structural changes in the sacroiliac joint (sacroiliitis) on x-ray, fulfilling the Modified New York classification criteria (mNY-positive) (van der Linden, 1984), whereas in those with nr-axSpA structural changes on conventional radiographs do not meet the mNY criteria (mNY-negative) (Rudwaleit, 2005; Dougados, 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. In the US, however, recent data suggest that the prevalence is similar to that of RA (axSpA: 0.7% to 1.4%; RA: 0.5% to 1.0%) (Reveille; 2012; Myasoedova, 2010; Helmick, 2008) and a cross sectional cohort study conducted in a UK primary care population to investigate the prevalence of inflammatory back pain (IBP) when applying the ASAS criteria (Hamilton et al, 2014) showed a minimum prevalence of IBP in a UK primary care population of 1.7%.

In patients with axSpA, the disease typically originates in the sacroiliac joints, then progresses to the spine. In the sacroiliac joints and the spine, active inflammation results in erosions, sclerosis, and fatty lesions. However, the most characteristic feature is new bone formation leading to ankylosis of the sacroiliac joints and syndesmophytes attached to the vertebral bodies. As a result of extended syndesmophyte formation, the spine may become fused over time. The majority of patients with axSpA have inflammatory back pain. Other 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, 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 develop structural damage or radiographic abnormalities involving their sacroiliac joints and may fulfill the mNY criteria for AS. However, the rate of development of structural damage varies among patients (Rudwaleit, 2012). Some patients develop bilateral sacroiliitis, some 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, 2013c).

Spondyloarthritides and inflammatory bowel disease (IBD) are chronic, idiopathic inflammatory disorders of, respectively, the axial and peripheral joints/entheses, and the intestinal tract, affecting up to 1% of our population. Typically, SpA manifests between adolescence and the age of 40. There is clinical and genetic evidence supporting some degree of overlap between the pathogenesis of these 2 entities. In SpA, microscopic gut inflammation can be present as an acute or a chronic inflammation. Normal histology of the gut or acute lesions, mimicking a bacterial colitis, were predominantly found in patients presenting with transient arthritis, whereas in

patients with chronic intestinal lesions similar to Crohn's disease (CD), a more persistent joint inflammation was perceived (Mielants et al, 1995). Microscopic gut inflammation was observed in about half of SpA patients originally in the 1980s and this prevalence has been confirmed in the Gent Inflammatory Arthritis and spoNdylitis cohort T (GIANT), which focused on new onset forms of SpA using the recently described ASAS classification criteria (Van Praet et al, 2013). Although about 6.5% of SpA patients evolved into IBD over 5 years, in patients exhibiting the chronic type of gut inflammation resembling Crohn's disease, this number rose to 20%.

2.2 Burden of disease in axial spondyloarthritis

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 costs associated with loss of work capacity (Kobelt et al, 2006; Kobelt et al, 2004; Boonen et al, 2003; Ward 2002).

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

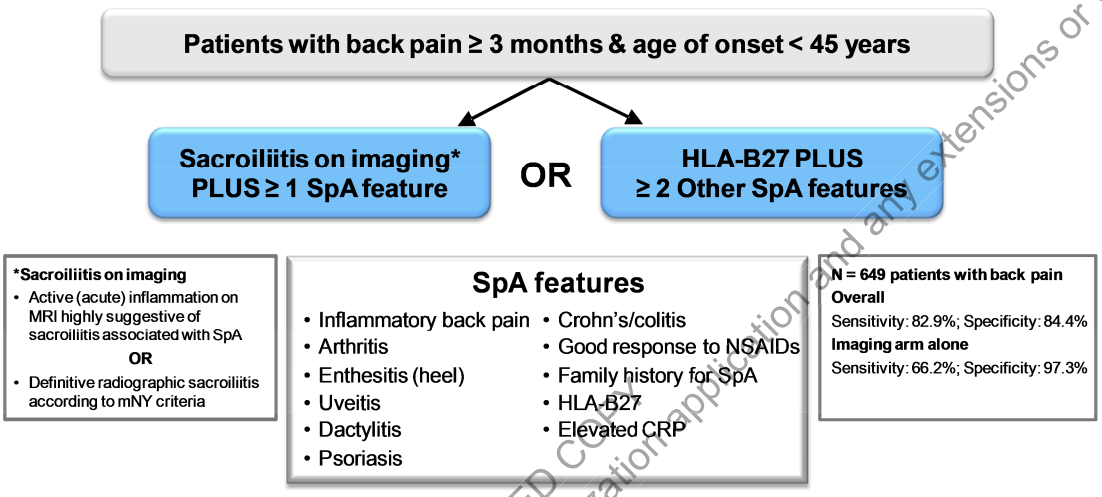
2.3 Diagnosing axial spondyloarthritis in clinical practice

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 whose sacroiliac joint (SIJ) x-rays do not have definitive evidence of sacroiliitis (Rostom, 2010). For a definitive classification of AS, the mNY classification criteria require radiographic evidence of sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3 to 4 unilaterally PLUS at least 1 of the following clinical criteria: low back pain and stiffness for ≥3 months, limitation of lumbar spine motion, or limitation of chest expansion. These criteria were designed for classification of patients in clinical studies rather than for diagnostic purposes. However, they have in fact been used for diagnosis resulting in diagnosis being delayed until irreversible structural damage documented on SIJ x-rays. Several publications have documented that the time from symptom onset to diagnosis of AS ranges from 5 to 10 years (Feldtkeller et al, 2003; Feldtkeller et al, 2000; van der Linden et al, 1984a), thus demonstrating that radiographic or x-ray changes lag far behind other signs and symptoms.

Due to the problem of delayed disease recognition, ASAS recently developed new classification criteria for axSpA that do not require the presence of definitive sacroiliitis on x-ray, thus identifying a nr-axSpA subpopulation (Rudwaleit et al, 2009c; Rudwaleit et al, 2009d). These criteria establish standards that apply to patients with or without radiographic sacroiliitis,

enabling the conduct of clinical studies in patients with both nr-axSpA and AS. In patients with a history of chronic back pain for ≥3 months and age of onset <45 years, a classification of axSpA can be made based on either 1) current evidence of sacroiliitis on imaging (radiographs or MRI) plus ≥1 typical SpA feature or 2) the presence of HLA-B27 plus ≥2 typical SpA-features (Figure 2.1). In these criteria, sacroiliitis is defined as MRI evidence of sacroiliac joint inflammation or radiographic evidence of sacroiliitis meeting mNY classification criteria (Rostom, 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.
Source: Rudwaleit et al, 2009d

2.4 Current management of axial spondyloarthritis

Based on the current treatment recommendations developed by ASAS and the European League Against Rheumatism (EULAR) for axSpA, first-line therapy consists of nonsteroidal anti-inflammatory drugs (NSAIDs) and nonpharmacologic treatment such as patient education and regular exercise/physiotherapy (Braun et al, 2011). NSAIDs are often initially 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 et al, 2011).

Patients who are intolerant of, or have inadequately responded to NSAIDs, or those in whom NSAIDs are contraindicated, have limited treatment options. Tumor necrosis factor alpha (TNFα) inhibitors (CZP, adalimumab [ADA], etanercept [ETN], infliximab [IFX], and golimumab [GOL]) are currently the only effective and approved treatment options. Infliximab and GOL are indicated for active AS only, while CZP, ADA, and ETN are indicated for nr-axSpA as an addition to the AS indication in several regions.

With the advent of the ASAS classification criteria for axSpA, several registration studies have been conducted in patients with nr-axSpA (Dougados et al, 2013; Sieper et al, 2013d) or axSpA (Landewe et al, 2014). These studies have found that anti-TNFs are effective in nr-axSpA patients, particularly in patients with objective signs of inflammation as defined by MRI positivity or CRP. The RAPID-axSpA study, the first axSpA study to enroll both AS and nr-axSpA patients, showed that baseline disease activity and treatment effect was 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 (Cimzia®) received approval in the EU and several other countries, eg, Turkey, Argentina, Russia, Chile, Switzerland, Hong Kong, Dominican Republic, Ecuador, and Peru, for the treatment of adult patients with severe active axSpA (comprising AS and nr-axSpA) and was approved for the treatment of adults with active AS in the USA, Canada, Australia, and also Malaysia.

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

2.5 Rationale

The demonstration of maintenance of response after reduction or even withdrawal of treatment would offer the physician and patient the opportunity to minimize the risks of anti-tumor necrosis factor (TNF) treatment while reducing healthcare costs. The data available to date suggest that anti-TNF therapy withdrawal in patients with active, nonradiographic, and/or early axSpA who are either in remission, or who have an ASAS40 response resulted in a flare (defined as loss of sustained remission, loss of ASAS40 response, or BASDAI >3 at 2 consecutive visits) in the majority (56 to 83%) of patients, resulting in the need to re-establish treatment (Haibel et al, 2013; Sieper et al, 2013a; Song et al, 2012). Publications that reported the effects of retreatment after a flare indicated that, in general, patients flaring responded well to retreatment. However, these studies did not provide information on questions such as whether there is an increased risk of immunogenicity following retreatment.

Available data suggest that the efficacy of anti-TNF treatment can be maintained even with reduction in dosage in a majority of patients with AS (Cantini et al, 2013; Olivieri et al, 2013). However, these studies suffer from several limitations and therefore there is a need to generate further robust data from prospective placebo-controlled, randomized studies to address the question of whether and in which patients dose reduction can be considered.

The AS0005 study introduces both a full withdrawal arm (placebo) as well as a half-dose arm (CZP 200mg Q4W) to assess a potential differential effect between both active treatment arms (full-dose and half-dose) and placebo. Furthermore, it will also provide data on the efficacy and safety of retreatment after subjects experience a flare in disease activity.

The treatment of axSpA with TNF-inhibitors is known to also have some beneficial impact on extra-articular manifestations, like uveitis, psoriasis, and IBD. AS0005 will provide data on the

frequency and severity of these comorbidities in the study population and whether CZP can improve the signs and symptoms of both the extra-articular manifestations and axSpA at the same time. For axSpA patients suffering from gut inflammation, the QoL will be assessed with an inflammatory bowel disease questionnaire (IBD-Q) and, in addition to this, an analysis of calprotectin in stool and serum samples (a protein associated with acute gut inflammation) will be performed to assess the correlation between gut inflammation, quality of life, and response to treatment with CZP.

3 STUDY OBJECTIVES

The following key definitions are provided as a reference for understanding the study objectives and are used throughout the protocol.

Sustained remission is achieved when a subject has an ASDAS <1.3 at Week 32 or Week 36 (if ASDAS <1.3 at Week 32, it must be <2.1 at Week 36 [or vice versa]) and at Week 48. A subject is eligible for Part B of the study only if sustained remission is achieved in Part A.

A flare occurs when a subject has an ASDAS ≥2.1 at 2 consecutive visits or ASDAS >3.5 at any visit during Part B.

Subjects who meet the criteria of flare during Part B and who crossed-over to full-dose treatment (CZP 200mg Q2W) are regarded as escapers.

3.1 Primary objective

The primary objective of the study is to evaluate the percentage of subjects who do not experience a flare on CZP 200mg Q2W (full-dose) or 200mg Q4W (half-dose) as compared to placebo (CZP withdrawal) during Part B.

3.2 Secondary objectives

The secondary objectives are to:

- Evaluate the percentage of subjects achieving sustained remission at the end of Part A
- For subjects randomized into Part B:
  - Evaluate the time to flare and other measures of signs and symptoms
  - Compare the percentage of subjects who do not experience a flare between CZP full-dose and half-dose
  - Evaluate the efficacy of re-initiation of treatment with the CZP full-dose in subjects who experience a flare following a withdrawal or dose reduction of CZP
- Assess safety and tolerability of CZP
- Evaluate inflammatory changes over time as assessed by MRI

3.3 Other objectives

The other objectives are to evaluate:

- Physical function
- Signs and symptoms of the disease

- Morning stiffness
- Fatigue
- Extra-articular manifestations of axSpA

- Health-related QoL
- Work and household productivity
- Subject's health status
- Direct medical resource utilization
- Correlation of fecal calprotectin, serum calprotectin, IBD-Q and CRP

3.4 Pharmacokinetic, pharmacogenomic, and immunological objectives

Pharmacokinetic and immunological objectives are to follow the CZP concentrations throughout the study as well as the evolution of immunogenicity, respectively. Other pharmacogenomic objectives are:

- Exploratory biomarkers and cytokines
- Possible genetics, genomics, and proteomics

4 STUDY VARIABLES

4.1 Efficacy variable

4.1.1 Primary efficacy variable

The primary efficacy variable is the percentage of subjects in Part B who do not experience a flare (refer to Section 3 for definition of flare).

4.1.2 Secondary efficacy variables

4.1.2.1 Secondary efficacy variables for subjects entering Part A

- Percentage of subjects achieving sustained remission at Week 48
- 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], and Ankylosing Spondylitis Disease Activity Score-very High Disease activity [ASDAS-vHD]) and clinical improvement (Ankylosing Spondylitis Disease Activity Score-Clinically Important Improvement [ASDAS-CII], Ankylosing Spondylitis Disease Activity Score-Major Improvement [ASDAS-MI]) at Week 48

4.1.2.2 Secondary efficacy variables for subjects entering Part B

The following are secondary efficacy variables for subjects entering Part B.

- Time to flare
- ASDAS disease activity (ASDAS-ID, ASDAS-MD, ASDAS-HD, and ASDAS-vHD) and clinical improvement (ASDAS-CII, ASDAS-MI) at Week 96

- ASAS20, ASAS40, ASAS5/6, and ASAS PR response at Week 96
- Change from Baseline in ASDAS, BASDAI, BASFI, and BASMI at Week 96
- BASDAI50 response at Week 96
- Change from Baseline in sacroiliac SPARCC and ASspIMRI-a in the Berlin modification scores at Week 96

4.1.2.3 Secondary efficacy variables for subjects who experience a flare in Part B

The following are secondary efficacy variables for subjects who experience a flare in Part B. These will be evaluated at Escape Week 12.

- ASDAS disease activity (ASDAS-ID, ASDAS-MD, ASDAS-HD, and ASDAS-vHD) and clinical improvement (ASDAS-CII, ASDAS-MI)
- ASAS20, ASAS40, ASAS5/6, and ASAS PR response
- Change from Baseline in ASDAS, BASDAI, BASFI, BASMI, and sacroiliac SPARCC and ASspIMRI-a in the Berlin modification scores.

4.1.3 Other efficacy variables

4.1.3.1 Other efficacy variables for subjects entering Part A

The following other efficacy variables for subjects entering Part A will be evaluated at all scheduled study visits where the assessment is performed through Week 48.

- ASAS20, ASAS40, ASAS5/6, and ASAS PR response
- BASDAI50 response
- Change from Baseline in ASDAS, BASDAI, and BASMI
- ASDAS disease activity (ASDAS-ID, ASDAS-MD, ASDAS-HD, and ASDAS-vHD) and clinical improvement (ASDAS-CII, ASDAS-MI)
- Change from Baseline in sacroiliac SPARCC and ASspIMRI-a in the Berlin modification scores
- Change from Baseline in all individual ASAS core components
  - Patient's Global Assessment of Disease Activity (PtGADA)
  - Total spinal pain (Numeric Rating Scale [NRS])
  - BASFI
  - Average of Questions 5 and 6 of the BASDAI concerning morning stiffness
- Change from Baseline in nocturnal spinal pain (NRS)
- Change from Baseline in spinal mobility, as assessed by occiput to wall distance
- Change from Baseline in spinal mobility as assessed by chest expansion
- Change from Baseline in PhGADA

- Change from Baseline in Fatigue (NRS) (from BASDAI)
- Change from Baseline in CRP
- Change from Baseline in ASQoL
- Change from Baseline in Work Productivity Survey (WPS)
- 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
- Change from Baseline in Maastricht Ankylosis Spondylitis Enthesitis Score (MASES)
- Change from Baseline in swollen and tender joint counts (44 joint count)
- Number of uveitis flares
- Number of IBD exacerbations
- Change from Baseline in fecal calprotectin
- Change from Baseline in serum calprotectin
- Change from Baseline in the IBD-Q
- Correlation between fecal calprotectin, serum calprotectin, IBD-Q, and CRP
- Number of psoriasis exacerbations (in subjects with concurrent psoriasis)
- Change from Baseline in all Short-Form 36-Item Health Survey (SF-36) domains, SF-36 Physical Component Summary (PCS), and SF-36 Mental Component Summary (MCS)
- Resources utilization: concomitant medical procedures, healthcare provider consultations not foreseen by the protocol, hospitalizations/emergency room visits

4.1.3.2 Other efficacy variables for subjects entering Part B

The following other efficacy variables for subjects entering Part B will be evaluated at all scheduled study visits where the assessment is performed following the first administration of study medication in Part B.

- ASAS20, ASAS40, ASAS5/6, and ASAS PR response
- BASDAI50 response
- ASDAS disease activity (ASDAS-ID, ASDAS-MD, ASDAS-HD, and ASDAS-vHD) and clinical improvement (ASDAS-CII, ASDAS-MI)
- Change from Baseline in ASDAS, BASDAI, and BASMI
- Change from randomization Baseline (Week 48) in ASDAS, BASDAI, BASFI, and BASMI
- Change from Baseline in all individual ASAS core components
  - PtGADA
  - Total spinal pain (NRS)

  - BASFI
  - Average of Questions 5 and 6 of the BASDAI concerning morning stiffness
- Change from Baseline in nocturnal spinal pain (NRS)
- Change from Baseline in spinal mobility, as assessed by occiput to wall distance
- Change from Baseline in spinal mobility assessed by chest expansion
- Change from Baseline in PhGADA
- Change from Baseline in Fatigue (NRS) (from BASDAI)
- Change from Baseline in CRP
- Change from Baseline in ASQoL
- Change from Baseline in sacroiliac SPARCC and ASspIMRI-a in the Berlin modification scores
- Change from randomization Baseline (Week 48) in sacroiliac SPARCC and spine ASspIMRI-a in the Berlin modification scores
- Change from Baseline in WPS
- Health status as assessed by the EQ-5D: domains, VAS actual score, and change from Baseline in VAS score
- Change from Baseline in MASES
- Change from Baseline in swollen and tender joint counts (44 joint count)
- Number of uveitis flares
- Number of inflammatory bowel disease exacerbations
- Change from Baseline in fecal calprotectin
- Change from Baseline in serum calprotectin
- Change from Baseline in the IBD-Q
- Correlation between fecal calprotectin, serum calprotectin, IBD-Q, and CRP
- Number of psoriasis exacerbations (in subjects with concurrent psoriasis)
- Change from Baseline in all SF-36 domains, SF-36 PCS, and SF-36 MCS
- Resources utilization: concomitant medical procedures, healthcare provider consultations not foreseen by the protocol, hospitalizations/emergency room visits

4.1.3.3 Other efficacy variables for subjects who experience a flare in Part B

The following other efficacy variables for subjects who experience a flare in Part B will be evaluated at all scheduled study visits where the assessment is performed following Escape Week 0.

- ASDAS disease activity (ASDAS-ID, ASDAS-MD, ASDAS-HD, and ASDAS-vHD) and clinical improvement (ASDAS-CII, ASDAS-MI)
- ASAS20, ASAS40, ASAS5/6, and ASAS PR response
- Change from Baseline in ASDAS, BASDAI, and BASMI
- Change from randomization Baseline (Week 48) in ASDAS, BASDAI, BASFI, and BASMI
- Change from the visit at which the flare occurred in ASDAS, BASDAI, BASFI, and BASMI
- Change from Baseline in all individual ASAS core components
  - PtGADA
  - Total spinal pain (NRS)
  - BASFI
  - Average of Questions 5 and 6 of the BASDAI concerning morning stiffness
- Change from Baseline in nocturnal spinal pain (NRS)
- Change from Baseline in spinal mobility, as assessed by occiput to wall distance
- Change from Baseline in spinal mobility assessed by chest expansion
- Change from Baseline in PhGADA
- Change from Baseline in Fatigue (NRS) (from BASDAI)
- BASDAI50 response
- Change from Baseline in CRP
- Change from Baseline in ASQoL
- Change from Baseline in sacroiliac SPARCC and ASspIMRI-a in Berlin modification scores
- Change from randomization Baseline (Week 48) in sacroiliac SPARCC and ASspIMRI-a in Berlin modification scores
- Change from Escape Week 0 in sacroiliac SPARCC and ASspIMRI-a in Berlin modification scores
- Change from Baseline in WPS
- Health status as assessed by the EQ-5D: domains, VAS actual score, and change from Baseline in VAS score
- Change from Baseline in MASES
- Number of uveitis flares
- Number of IBD exacerbations
- Change from Baseline in fecal calprotectin
- Change from Baseline in serum calprotectin

- Change from Baseline in the IBD-Q
- Correlation between fecal calprotectin, serum calprotectin, IBD-Q, and CRP
- Number of psoriasis exacerbations (in subjects with concurrent psoriasis)
- Change from Baseline in all SF-36 domains, SF-36 PCS, and SF-36 MCS
- Resources utilization: concomitant medical procedures, healthcare provider consultations not foreseen by the protocol, hospitalizations/emergency room visits

4.2 Pharmacokinetic and pharmacogenomic variables

4.2.1 Pharmacokinetic variables

Plasma concentrations of CZP will be measured at Baseline and subsequent timepoints as described in Table 5.1 and Table 5.2. These plasma samples may be used additionally for analyses of CZP and its constituent moieties using alternative methods.

4.2.2 Biomarkers

Selected samples collected for measurement of CZP plasma concentration may be used additionally for analyses of biomarkers and cytokines. These analyses may include, but are not limited to: Matrix metalloproteinase-3 (MMP-3); bone morphogenic protein (BMP) BMP-2, -4 and -7, wingless-related mouse mammary tumor virus integration site protein (WNT1), Inducible Signaling Pathway proteins (WISP), Gremlin, Dickkopf-related protein 1 (DKK1), Sclerostin, Hedgehog proteins (Shh, Ihh, Dhh), Collagen turnover/cleavage products, collagen type X, vascular endothelial growth factor (VEGF), citrullinated vimentin fragments, cytokines: IL13, IL17 A and F, IL23, IL34, Transforming Growth Factor (TGF)β, Macrophage colony-stimulating factors (M-CSF), Granulocyte macrophage colony-stimulating factor (GM-CSF, CSF-1, soluble CSF-1 Receptor (sCSF1r) levels.

4.2.3 Pharmacogenomic variables

Blood samples will be drawn for possible genetic, genomic, and proteomic analysis at Baseline, and, for genomic and proteomics analysis only, additionally at Weeks 12, 24, 48, 72, and 96/WD to enable exploratory evaluation of biomarkers relative to drug treatment and inflammatory and immune response processes. The samples will be stored at -80°C at the Central Biorepository for up to 20 years or according to local laws.

4.3 Immunogenicity variables

Anti-CZP antibody (ADAb) levels will be assessed at Baseline and subsequent timepoints as described in Table 5.1 and Table 5.2.

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

4.4 Safety variables

Safety variables to be assessed are AEs, physical examination, vital sign measurements, chest x-ray, and measurements of laboratory parameters (hematology, biochemistry, and urinalysis).

Adverse events will be solicited at every visit, and recorded and coded according to the latest version of the Medical Dictionary for Regulatory Activities® criteria used at UCB at the time of analysis.

Physical examination findings will be recorded in the electronic Case Report Form (eCRF) only at Screening. Clinically relevant changes in subsequent physical examinations will be recorded as AEs.

Clinical laboratory values (hematology, biochemistry, and urinalysis) will be collected and assessed at Screening, Baseline, at Weeks 12, 24, 32, 36, and every 12 weeks thereafter through to study Week 96/WD Visit and at the SFU Visit 10 weeks after the last dose of study medication. C-reactive protein values will be collected and assessed at Screening, Baseline, Weeks 2, 4, 12, 24, 32, 36, 3 to 5 days prior to Week 48, Week 50, Week 52, and every 4 weeks thereafter through to study Week 96/WD Visit. For escapers, different schedules for clinical laboratory values and CRP apply after start of the escape treatment (refer to Table 5.2).

At Screening, Week 48, and Week 96, all subjects will have an IGRA test (QuantiFERON TB GOLD In Tube test or another WHO-validated IGRA test such as Elispot, if QuantiFERON TB GOLD In Tube test is not available locally). A chest x-ray (or, if done, computed axial tomography of the chest) at Screening (or up to 3 months prior to Screening) must be read and reported consistent with standard clinical reporting practice by an experienced 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, including the Week 96/WD Visit, for signs and symptoms of latent or active TB infection and risk factors for exposure to TB using the TB questionnaire.

5 STUDY DESIGN

5.1 Study description

Study AS0005 is a multicenter, open-label (Part A) followed by a randomized, double-blind, parallel-group, placebo-controlled clinical study (Part B) to evaluate the efficacy, safety, PK, and immunogenicity of CZP in adult subjects with axSpA in sustained remission who continued either on full-dose treatment (CZP 200mg Q2W), on a dose reduction (CZP 200mg Q4W), or withdrawal of CZP treatment.

The study includes 2 parts, A and B, as follows (a schematic diagram is provided in Figure 5.1 and the schedule of study assessments is in Table 5.1 and Table 5.2).

5.1.1 Part A

Period 1 (Screening Period): Up to 5 Weeks before Baseline

Eligible subjects will be informed about the study and sign the informed consent. Concomitant medications such as MTX, SSZ, hydroxychloroquine (HCQ), NSAIDs, and corticosteroids, will be verified and, if required, the washout of any medications not permitted for use during the study will be started. Concomitant medications must follow the protocol requirements in Table 6.1. Subjects will receive a physical examination and vital signs measurements will be

taken. Women of childbearing age will be tested for pregnancy. Laboratory data (hematology, urine, and biochemistry tests) and treatment of latent TB (LTB), where necessary, will be collected. Subjects must undergo a TB test and complete a TB questionnaire. Patient's Global Assessment of Disease Activity, BASDAI, BASMI, spinal mobility assessments, and MRI will be performed. Additionally, a central reading of the x-ray will define the stratification of the subjects into the nr-axSpA or the AS subpopulation.

Period 2 (Open-Label Period): Week 0 (Baseline) to Week 48

Eligible subjects will receive 3 loading doses of CZP sc 400mg at Weeks 0, 2, and 4 followed by CZP 200mg Q2W.

All subjects will be trained on self-administration at Weeks 2 and 4. Subjects will self-administer starting from Week 6. At Weeks 12, 24, 32, 36, 3 to 5 days prior to Week 48 Visit and Week 48 in Period 2, subjects will visit the site and undergo relevant tests and assessments according to Table 5.1. The injection schedule (Figure 7.1) will provide the sequence of self-administration and site visits including administration at the site.

All subjects who have not achieved sustained remission at the end of Period 2 (Week 48) will be discontinued from the study and treated at the discretion of their physician. Those subjects who discontinue prematurely from the study for any reason will be treated at the discretion of their physician.

5.1.2 Part B

Period 3 (Double-Blind Period): Week 48 to Week 96, placebo-controlled

Subjects must meet the sustained remission criteria as defined in Section 3 in order to be randomized to Part B.

Subjects in sustained remission will be randomized in a 1:1:1 ratio to the following treatment arms:

- CZP administered sc at a dose of 200mg Q2W (full-dose)
- CZP administered sc at a dose of 200mg Q4W (half-dose)
- Placebo

To maintain the study blind during Part B, study medication administration will be done by a dedicated trained unblinded study team at each site. In order to reduce the number of onsite visits for the subjects, where possible, a home nurse service will be offered. Home nurses, who will be responsible for administering the study medication at the subject's home, will be unblinded.

All subjects who discontinue prematurely from the study for any reason during the Double-Blind Period will be treated at the discretion of the Investigator.

The last dosing visit will be performed according to the dosing schedule in Table 5.1. The final study assessments will be performed at Week 96. Subjects experiencing a flare during the Double-Blind Period will receive escape treatment as defined in Section 5.1.3.

Stool samples for fecal calprotectin will be collected for all subjects at Weeks 48 and 96/WD and blood samples for serum calprotectin will be collected for all subjects 3 to 5 days prior to Week 48, Week 72, and at Week 96/WD.

Period 4 (SFU Period): 10 weeks after the last dose of study medication

All subjects, including those withdrawn from study treatment, will have a SFU Visit 10 weeks after their last dose of study medication.

5.1.3 Escape treatment

Subjects receiving placebo or half-dose CZP who experience a flare during the Double-Blind Period will escape to full-dose treatment until the end of that period or for at least 12 weeks, whichever is longer. Subjects who experience a flare while on CZP full-dose will continue to receive CZP full-dose (see details in Section 6.3.2). The interactive voice or web response system (IXRS) will be used to determine whether flare criteria are met.

The schedule of study assessments for subjects experiencing a flare in Part B is provided in Table 5.2.

5.1.4 Study duration per subject

For each subject, the study will last a maximum of 109 weeks, as follows:

- Up to 5 weeks of Screening Period
- 48 weeks in the Open-Label Period
- 48 weeks in the Double-Blind Period (dose reduction/withdrawal of CZP-treatment)
- A SFU Visit 10 weeks after last dose administration (Period 4).

Of the 10 weeks interval specified for the SFU Visit, the first 2 weeks coincide with the last 2 weeks of the Double-Blind Period (ie, last 2 weeks of the 48 weeks) and the last administration is at Week 94. Hence, the maximum duration is 109 weeks.

For subjects who experience a flare during the Double-Blind Period, the study duration might be prolonged (refer to Section 6.3.2).

The end of the study is defined as the date of the last visit (SFU) of the last subject in the study.

5.1.5 Planned number of subjects and sites

Approximately 1250 subjects will be screened in order to enroll 750 subjects into Part A, where 210 subjects are expected to meet the sustained remission criteria and be eligible for randomization into Part B. Ankylosing Spondylitis Disease Activity Score will be closely monitored during Part A of the study to project the percentage of enrolled subjects likely to achieve sustained remission at the end of Part A. The enrollment will be adjusted accordingly in order to achieve the required number of 210 subjects in sustained clinical remission qualifying for Part B.

It is planned to enroll subjects at approximately 95 sites.

5.1.6 Anticipated regions and countries

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

5.2 Schedule of study assessments

The schedule of study assessments for all subjects completing Part A and Part B of the study is presented in Table 5.1.

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Week (W)	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU[b]**
Protocol Activity																										
Inclusion/exclusion	X	X																								
Informed consent [c]	X																									
Demographic data	X																									
Medical history (including axSpA and extra-articular manifestations history)	X																									
Vital signs [d]	X	X	X	X		X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X
Hematology/urine/ biochemistry	X[e]	X				X		X		X		X		X					X		X		X		X	X
CRP [f]	X	X	X	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	
Pregnancy testing [g]	X	X																							X	X
PE [h]	X	X				X		X				X			X				X		X		X		X	X
Extra-articular assessments	X	X		X		X		X				X			X		X		X		X		X		X	
Chest x-ray [i]	X																									
TB test [j]	X														X										X	
TB questionnaire	X	X				X		X				X			X				X		X		X		X	
Sacroiliac joint x-ray [k]	X																									
MRI [l]	X														X										X	

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Week (W) / **Protocol Activity**	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU[b]**
Stool sample [m]		X													X										X	
Serum calprotectin		X				X		X						X							X				X	
IBD-Questionnaire		X												X											X	
BASMI and Spinal mobility [n]	X	X	X	X		X		X				X			X		X		X		X		X		X	
BASDAI [f]	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	
SF-36		X		X		X		X				X		X					X		X		X		X	
AsQoL		X	X	X		X		X				X		X					X		X		X		X	
EQ-5D		X				X		X				X		X					X		X		X		X	
MASES		X				X		X				X			X				X		X		X		X	
Total and nocturnal spinal pain		X	X	X		X		X				X		X			X		X		X		X		X	
Swollen and tender joint counts		X	X	X		X		X				X			X		X		X		X		X		X	
Patient's Global Assessment of Disease Activity [f]	X	X	X	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	
Physician's Global Assessment of Disease Activity		X				X		X				X			X		X		X		X		X		X	
Work Productivity		X		X		X		X				X			X				X		X		X		X	

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Week (W) / **Protocol Activity**	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU[b]**
Survey																										
Resources utilization [o]		X				X		X				X			X				X		X		X		X	
CZP plasma concentration/ ADAb		X		X		X		X						X					X		X		X		X	X
Biomarker		X		X		X		X						X					X		X		X		X	X
Genetics		X												X												
Genomics/ proteomics		X				X		X						X							X				X	
Prior and Concomitant medication[p]	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
IXRS	X	X	X	X		X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X
Study drug sc onsite		X	X	X		X		X		X		X			X		X		X		X		X			
Study drug sc self-inj. at home					X		X		X		X		X													
Randomization															X											
Nurse visit at subj. home (incl. study drug sc inj.) [q]																X		X		X		X		X		

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A													PART B										
Study Period	**1 (Screening)**	**2 (Open-Label)**												**3 (Double-Blind)**										**4**
Week (W) / **Protocol Activity**	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU [b]**
Check of sustained remission criteria [r]						X		X		X		X			X	X	X	X	X	X	X	X	X	X		
Telephone Contact [s]					X		X		X				X													

Abs=antibodies; ADAb= anti-CZP antibody; AEs=adverse events; AS=ankylosing spondylitis; AsQoL=Ankylosing Spondylitis Quality of Life; axSpA=axial spondyloarthritis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; CZP=certolizumab pegol; EQ-5D=EuroQoL Health Status Questionnaire; H=home, no site visit; HIV=human immunodeficiency virus; HLA-B27=human leukocyte antigen B27; HN=home nurse visit at subject's home; IBD=Inflammatory bowel disease; incl.=including; inj=injection; IXRS=Interactive Voice or Web Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MRI=magnetic resonance imaging; PE=physical exam; sc=subcutaneously; SF-36=Short-Form 36-item Health Survey; SFU=Safety Follow-Up; SI=sacroiliac; subj=subject; TB=tuberculosis; W=Week; WD=Withdrawal; WHO=World Health Organization

[a] Assessments conducted 3 to 5 days prior to Week 48 will serve as the qualification assessments for subjects determined to be eligible for randomization into Part B at Week 48.

[b] SFU: 10 weeks after last dose of study medication.

[c] 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 be obtained from subjects consenting also to the use of their blood samples for possible genetic, genomic, and proteomic analysis.

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

[e] Testing to rule out hepatitis B surface antigen, antibodies to hepatitis C, antibodies to HIV and HLA-B27 at Screening only.

[f] To be assessed as indicated and from Week 52 onwards every 4 weeks only.

[g] Pregnancy testing for women of childbearing potential will be serum testing at the Screening Visit and SFU and urine testing at Baseline and Week 96/WD Visit.

[h] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Weight is to be measured at Screening, Baseline, Week 48, and at Week 96/WD. Height will be measured at the Baseline Visit only.

[i] Screening chest x-ray must have occurred within 3 months prior to Screening or during Screening, and should be repeated only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure).

[j] QuantiFERON TB GOLD test or another WHO-validated IGRA test such as Elispot test, if QuantiFERON TB GOLD test is not locally available. The TB test will be repeated at Week 48 and 96 (or at WD Visit if medically indicated) for subjects with previously negative TB test result.

[k] Sacroiliac joint x-rays will be performed at Screening and used as the Baseline assessment for all subjects. An SIJ x-ray performed ≤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.
[l] Magnetic resonance imaging of the spine and sacroiliac joints to be performed at Screening, and within a ± 2 weeks time window at Weeks 48 and 96 or WD Visit if the last MRI was performed more than 12 weeks prior to WD Visit.
[m] Kit for collection of stool sample to be provided at Screening Visit. Stool sample shall be obtained prior to Baseline and provided to the Investigator at the Baseline Visit.
[n] Occiput to wall distance; chest expansion; and BASMI, which includes modified Schober test, lateral spinal flexion, cervical rotation, tragus to wall distance, and maximal intermalleolar distance.
[o] Resource utilization includes: concomitant medical procedures, health care provider consultations not foreseen by the protocol, hospitalizations/emergency room visits.
[p] Prior medication will be at Screening only.
[q] Nurse visit at home only where approved and with agreement of subjects. Otherwise, the visit procedures will be done onsite by the site staff.
[r] Refer to Protocol Section 3 for definition. In case of loss of sustained remission in Part B, the subject must visit the study site for the next scheduled dose of study medication. The Investigator will initiate the escape treatment as appropriate. Refer to Table 5.2 for details.
[s] Subjects will be contacted by telephone about every 4 weeks in between the onsite visits.

Subjects experiencing a flare in Part B will be invited for an onsite visit to receive the next planned dose of investigational product (escape treatment). This visit will take place 2 weeks after the last assessment that resulted in meeting the flare criteria; or, at the discretion of the Investigator, at an earlier timepoint. As the start of escape treatment may vary from subject to subject, it will be referred to as "Escape Week 0" in Table 5.2. Subjects will remain on the escape treatment for at least 12 weeks or until Week 96 of the regular visit schedule as described in Table 5.1, whichever is longer.

The assessment schedule for subjects experiencing a flare in Part B will start 2 weeks after the flare condition is confirmed and will end 2 weeks before Week 96 after Baseline of the regular assessment schedule (Table 5.2). If the flare occurs late in Part B (at or after Week 82), the subject must receive the escape treatment for 12 weeks (eg, starting at Week 84 until Week 96). The final assessments at study end (as laid down for Week 96) must be performed 2 weeks after the last study dose administration (Table 5.1).

Table 5.2: Schedule of study assessments for all subjects experiencing a flare in Part B

	Part B for subjects experiencing a flare					
Study-Period	**3B**					
Visit / week (W) on escape treatment	**0**	**2**	**4**	**6 to 10 H/HN [a]**	**12 (and every 12 weeks thereafter) [b]**	**every 2 weeks in between [c] H/HN [a]**
Protocol Activity						
Vital signs [d]	X	X	X		X	
Hematology/urine/ biochemistry	X				X	
CRP [e]	X	X	X	X [f]	X	X [f]
Stool sample [g]	X				X	
Serum calprotectin [g]	X				X	
IBD-Questionnaire [g]	X				X	
PE	X	X	X		X	
Extra-articular assessments	X		X		X	
MRI [h]	X				X	
TB questionnaire	X				X	
BASMI & Spinal mobility [i]	X	X	X		X	
BASDAI	X	X	X	X [f]	X	X [f]
BASFI	X	X	X		X	
SF-36	X		X		X	
AsQoL	X	X	X		X	
EQ-5D	X		X		X	

Table 5.2: Schedule of study assessments for all subjects experiencing a flare in Part B

	Part B for subjects experiencing a flare					
Study-Period	3B					
Visit / week (W) on escape treatment	**0**	**2**	**4**	**6 to 10 H/HN [a]**	**12 (and every 12 weeks thereafter) [b]**	**every 2 weeks in between [c] H/HN [a]**
Protocol Activity						
MASES	X	X	X		X	
Total and nocturnal spinal pain	X	X	X		X	
Patient's Global Assessment of Disease Activity	X	X	X	X [f]	X	X [f]
Physician's Global Assessment of Disease Activity	X	X	X		X	
Work Productivity Survey	X		X		X	
Resources utilization [j]	X		X		X	
CZP plasma concentration/ADAb	X	X	X		X	
Biomarker	X	X	X		X	
Concomitant medication	X	X	X		X	
AEs	X	X	X		X	
IXRS	X	X	X	X	X	X
Study drug sc onsite	X	X	X		X	
Study drug sc self-inj. at home				X		X
Telephone Contact [k]				X		X

Abs=antibodies; ADAb=anti-CZP antibody; AEs=adverse events; AS=ankylosing spondylitis; AsQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; CZP=certolizumab pegol; EQ-5D=EuroQoL Health Status Questionnaire; H=home, no site visit; HN=home nurse visit at subjects home; IBD=Inflammatory bowel disease; IXRS=Interactive Voice or Web Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MRI=magnetic resonance imaging; PE=physical exam; sc=subcutaneously; SF-36=Short-Form 36-item Health Survey; TB=tuberculosis; W=Week

[a] HN Q4W only for obtaining blood sample (CRP) and electronic patient reported outcome (ePRO) data as indicated

[b] Schedule onsite visit every 12 weeks until Week 96 of regular visit schedule is reached. For example, at Weeks 74 and 86, if start of escape treatment is at Week 62 (=Escape Week 0). At Week 96 and SFU, perform assessments as described in Table 5.1. For subjects experiencing a flare at/after Week 82, escape treatment should be provided for 12 weeks and the subject invited for the final assessment visit (as laid down for Week 96) 2 weeks later

[c] Until 2 weeks before Week 96 of regular visit schedule is reached

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

[e] To be assessed as indicated and from Week 52 onwards every 4 weeks only

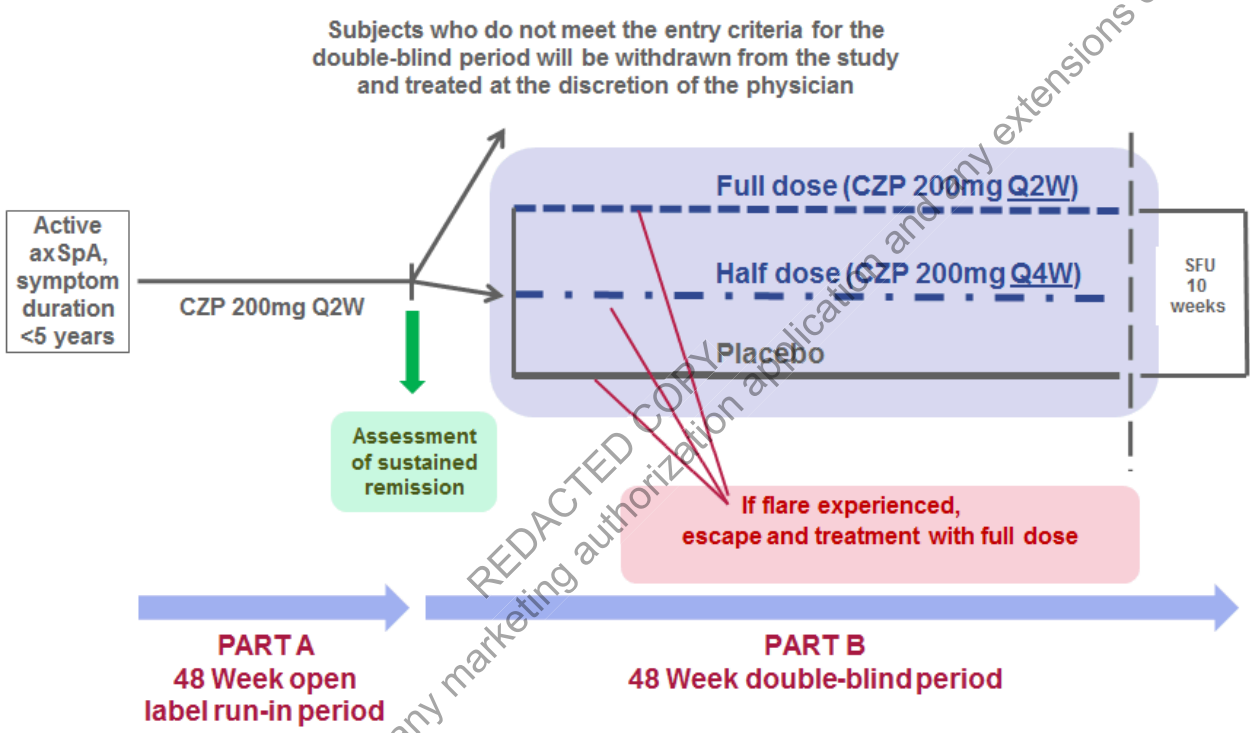
[f] To be assessed every 4 weeks only (Weeks 8, 12, 16, 20, 24, … up to Week 96)

[g] To be assessed at escape Weeks 0 and 12 only

[h] To be performed at escape Weeks 0 and 12 only and at final assessment visit at Week 96, if the last MRI was done at least 12 weeks prior to Week 96. Magnetic resonance imaging is to be performed within a ±2 weeks time window.
[i] Occiput to wall distance; chest expansion; and BASMI, which includes modified Schober test, lateral spinal flexion, cervical rotation, tragus to wall distance, and maximal intermalleolar distance
[j] Resource utilization includes: concomitant medical procedures, health care provider consultations not foreseen by the protocol, hospitalizations/emergency room visits
[k] Subjects will be contacted by telephone about every 4 weeks in between the onsite visits

5.3 Schematic diagram

Figure 5.1: Schematic diagram



axSpA=axial spondyloarthritis; CZP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks; SFU=Safety Follow-Up

5.4 Rationale for study design and selection of dose

There are limited data around the optimal duration of treatment in patients with early axSpA and whether it is appropriate to withdraw or reduce treatment at some point in patients who are in remission or low disease activity. The data available to date suggest that anti-TNF therapy withdrawal in patients with active, nonradiographic, and/or early axial spondyloarthritis who are either in remission, or who have an ASAS40 response resulted in a flare (defined as loss of sustained remission, loss of ASAS40 response, or BASDAI >3 at 2 consecutive visits) in the majority (56 to 83%) of patients, resulting in the need to re-establish treatment (Song, 2012; Haibel, 2013; Sieper et al, 2013a). Publications that reported the effects of retreatment after a flare indicated that, in general, patients flaring responded well to retreatment. However, these studies did not provide information on aspects such as whether there is an increased risk of immunogenicity following retreatment. The efficacy of anti-TNF treatment can be maintained

with reduction in dosage in a majority of patients with AS (Cantini et al, 2013; Olivieri et al, 2013). However, there is currently limited evidence related to the impact of dose reduction in patients with early axSpA.

The dose of CZP that will be used in this study is 200mg Q2W with a loading dose of CZP 400mg at Weeks 0, 2, and 4. Although there are 2 approved doses for rheumatologic disease in most regions around the world (loading dose of 400mg CZP at Weeks 0, 2, and 4 followed by CZP 200mg Q2W; 400mg Q4W can be considered), the CZP 200mg Q2W dose is the dose most frequently prescribed around the world. Thus, using the 200mg Q2W dose in this study will provide treating physicians around the world the opportunity to compare the study results with the dose they are most likely to use in their daily practice.

In order to ensure that subjects in the placebo arm or 200mg Q4W arm are not deprived of therapy in case of deterioration of their signs and symptoms, they will be offered escape opportunities to full-dose treatment (CZP 200mg Q2W) during the Double-Blind Period until the end of that period or for at least 12 weeks, whichever is longer.

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 by the parent(s) or legal representative.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.
3. Subject is at least 18 years old and not older than 45 years at the start of 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 (including 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 after the last dose of study treatment for at least 10 weeks (or - for participating countries of the European Union - 5 months in accordance with the Summary of Product Characteristics [SmPC]) or longer, if required by local regulations after the last dose of study treatment. Male subjects must agree to ensure that also their female partner(s) use adequate contraception during the study and for at least 10 weeks (or - for participating countries of the European Union - 5 months in accordance with the SmPC) or longer, if required by local regulations after the subject receives their last dose of study treatment.
5. Subjects must have a documented diagnosis of adult-onset axSpA with at least 3 months' symptom duration and meet the ASAS classification criteria for axSpA (according to Appendix 18.1) and symptom duration of less than 5 years prior to the participation of this study.
6. Subjects must have active disease at Screening as defined by

- ASDAS score ≥2.1
- BASDAI score ≥4
- Spinal pain ≥4 on a 0 to 10 NRS (from BASDAI Item 2)
- for mNY-negative subjects only: CRP> upper limit of normal (ULN) and/or current evidence for sacroiliitis on the Screening MRI as defined by a ASAS/Outcome Measures in Rheumatology Clinical Trials (OMERACT) SI-MRI score ≥2 and confirmed by central reading

7. 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 five 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.

AxSpA disease-related exclusions

6. Subjects must not have fibromyalgia or total spinal ankylosis ("bamboo spine"), or any other inflammatory arthritis, eg, RA, systemic lupus erythematosus, sarcoidosis.
7. 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 medication on the subject's primary diagnosis of axSpA.

Prior medications exclusions

8. Subjects must not have used the following medications in the manner as detailed by the Exclusion Criteria in the following table.

Table 6.1: 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 postscreening visit. Stable dose of analgesics (including narcotics) are permitted throughout the study.
NSAIDs (including cyclooxygenase 2 [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 postscreening visit. NSAID dose can be down-titrated at Investigator discretion, if clinically indicated, until Week 28, after which NSAID treatment should remain as stable as possible. NSAID dose should be stable until Week 96 (if subjects have to decrease or stop taking medication due to safety reasons, they may reduce their dose and continue in the study).
Oral corticosteroids	Maximum allowed ≤10mg daily total prednisone equivalent [a]	Any change in stable dose used for axSpA in the 28 days prior to the Baseline Visit.	A change in the dose is not allowed until Week 96. Oral corticosteroid tapers of less than 14 days used to treat other indication (asthma exacerbation, contact dermatitis, etc) are allowed as long as the maximum daily dose is ≤20mg. The taper must end at least 1 week before study visit.
Intramuscular (im) corticosteroids	Any dose	Use in the 28 days prior to the Baseline Visit.	Intramuscular corticosteroids must not be used during the study.

Table 6.1: Concomitant Medications (Prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
Intra-articular (ia) corticosteroids	Up to maximum approved dose	Use in the 28 days prior to the Baseline Visit.	SIJ ia corticosteroid injections are not allowed during the study. Peripheral joint injections are permitted.
Intravenous (iv) corticosteroids	Up to maximum approved dose	Use in the 28 days prior to the baseline Visit.	iv doses of corticosteroids 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, Week 48, or Week 96 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.	After Baseline ia injection of hyaluronic acid may be used in the knee.
SAARDs[b]: SSZ and/or HCQ and/or MTX and/or LFN and /or AZA	Maximum allowed: SSZ ≤3g daily HCQ ≤400mg daily MTX ≤25mg weekly AZA ≤150mg/day LFN ≤20mg/day	SAARD use initiated and/or any change in the dose regimen in the 28 days prior to the Baseline Visit. No change is permitted in the route of administration for MTX (im, sc, or oral) in the 28 days prior to the Baseline Visit	SAARDs should be stable until Week 96 (if a subject has to decrease or stop taking medications due to safety reasons, they may reduce their SAARDs and continue in the study).
SAARDs: Cyclosporine, Cyclophosphamide, Mycophenolic acid, Apremilast	Up to maximum approved dose	Use within 28 days prior to the Baseline Visit.	Must not be started during the study.

Table 6.1: Concomitant Medications (Prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria	Study Visits
Anti-TNF therapies: IFX ADA ETN GOL CZP	Any dose	For IFX, ADA, and GOL, any use within the 3 months prior to the Baseline Visit. For CZP any exposure history. For ETN, use within the 28 days prior to the Baseline Visit. Only 1 previous biologic is allowed.	Must not be started during the study.
Other rheumatologic therapies: Abatacept tocilizumab ustekinumab tofacitinib Rituximab or other anti-CD20 antibodies	Any dose	Any exposure history.	Must not be started during the study.
Osteoporosis Medications: Risedronate, Alendronate, Ibandronate Denosumab Cathepsin K inhibitor Cinacalcet Calcitonin	Up to maximum approved dose	All stable osteoporosis medications are permitted except for iv bisphosphonates.	Osteoporosis medications with the exception of iv bisphosphonates are allowed without restriction. iv bisphosphonates are not permitted any time within the study.
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.

ADA=adalimumab; AZA=azathioprine; axSpA=axial spondyloarthritis; CD20=Cluster of Differentiation 20; COX 2=cyclooxygenase 2; CZP=certolizumab pegol; ETN=etanercept; GOL=golimumab; HCQ=hydroxychloroquine; IFX=infliximab; ia=intra-articular; im=intramuscular; iv=intravenous; LFN=leflunomide; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; prn=pro re nata (as needed); RA=rheumatoid arthritis; SAARD=slow acting antirheumatic drug; SIJ=sacroiliac joint; SSZ=sulfasalazine

[a] A table of corticosteroid equivalent doses is provided in Table 18.1 (Appendix 18.2)

[b] Throughout the table, we refer to compounds such as sulfasalazine and methotrexate as SAARDs (slow-acting antirheumatic drugs). 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.

Previous clinical studies and previous biological therapy exclusions

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

Medical History Exclusions

13. Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the study or within 10 weeks (or – for participating countries of the EU – 5 months in accordance with the SmPC) following the last dose of the investigational product.
14. Subjects with a history of chronic or recurrent infections (more than 3 episodes requiring antibiotics or antivirals during the preceding year), recent serious or life-threatening infection within the 6 months prior to the Baseline Visit (including hospitalization for any infection in the last 6 months or any current sign or symptom that may indicate an infection).
15. Subjects with a history of herpes zoster infection within 6 months prior to the Baseline Visit.
16. Subjects with known TB infection, at high risk of acquiring TB infection, or LTB infection are excluded.
    a. Known TB infection whether present or past is defined as:
        - Active TB infection or clinical signs and symptoms suggestive of TB (pulmonary or extra pulmonary)
        - History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection
        - 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:
        - Known exposure to another person with active TB infection within the 3 months prior to Screening
        - 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 12.7.3 for further details and instructions.

17. Subjects with current acute or chronic viral hepatitis B or C or with human immunodeficiency virus (HIV) infection.
18. Subjects with current or a history of active infection with histoplasma, coccidiodes, paracoccidioides, pneumocystis, nontuberculous mycobacteria, blastomyces, or aspergillus.
19. Subjects must not have had a history of an infected joint prosthesis any time.
20. Subjects receiving any live (includes attenuated) vaccination within the 8 weeks prior to Baseline (eg, inactivated influenza and pneumococcal vaccines are allowed but nasal influenza vaccination is not allowed).
21. Subjects who, in the Investigator's opinion, have a high risk of infection (eg, subjects with leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections, and subjects who are permanently bedridden or wheelchair bound).
22. Subjects with a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.
23. Current malignancy or a history of malignancy, although subjects with less than 3 completely excised basal cell carcinomas or with cervical carcinoma *in situ* successfully surgically treated more than 5 years prior to Screening may be included.
24. Subjects with Class III or IV congestive heart failure as per the New York Heart Association (NYHA) 1964 criteria.
25. Subjects with a history of or suspected demyelinating disease of the central nervous system (eg, multiple sclerosis or optic neuritis).
26. Subjects who have had major surgery (including joint surgery) within 8 weeks prior to Screening or have planned surgery within 6 months of the Screening Visit.
27. Subjects with current or history of severe, progressive, and/or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, or neurological disease, as determined by the Investigator.
28. Subjects with significant laboratory abnormalities included but not limited to:
    - Liver function tests >2.0 x ULN
    - Estimated Glomerular Filtration Rate (GFR) as measured by Chronic Kidney Disease Epidemiology Collaboration (Levey et al, 2009) <60 mL/min/1.73m^2
    - White blood cell (WBC) <3.0x10^9/L
29. Subjects with any other condition that, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study.

6.3 Withdrawal and escape criteria

6.3.1 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 takes prohibited concomitant medications as defined in this protocol.
4. Subject withdraws his/her consent.
5. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
6. The Sponsor or a regulatory agency requests withdrawal of the subject.
7. Subject's subsequent TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure) and further examinations result in a diagnosis of active TB, or in case of LTB no prophylactic treatment was initiated. Refer to Section 12.7.3 for further details and instructions.

Once withdrawn from study treatment, subjects must return for the WD Visit, complete all WD assessments, and complete a final SFU Visit 10 weeks after the last dose of study medication.

Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered as lost to follow-up, the Investigator should make an effort (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), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The Case Report form must document the primary reason for withdrawal or discontinuation.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

Subjects withdrawn from the study will not be replaced.

6.3.2 Escape treatment

Subjects receiving placebo or half-dose CZP (200mg Q4W) who experience a flare during the Double-Blind Period will escape to full-dose treatment (CZP 200mg Q2W) until the end of that period or for at least 12 weeks, whichever is longer. The escapers need to come back to the site at the timepoint of the escape (Week 0), 2 and 4 weeks after escape (Weeks 2 and 4), and every 12 weeks thereafter until the originally scheduled Week 96.

Subjects escaping from placebo to full-dose CZP (200mg Q2W) will receive a loading dose of CZP (400mg Q2W; 2 injections) at the 3 consecutive visits after the flare. Subjects escaping

from half-dose CZP to full-dose CZP will receive a loading dose of CZP 200mg Q2W at the 3 consecutive visits after the flare. In order to maintain the blind, subjects escaping from half-dose CZP to full-dose CZP will receive a placebo administration and a CZP 200mg administration (a total of 2 injections) at these 3 visits (Figure 7.1).

Subjects randomized to the CZP full-dose (200mg Q2W) treatment during the Double-Blind Period who qualify for escape will remain on their current treatment allocation. As with subjects escaping from half-dose CZP to full-dose CZP, these subjects will receive a placebo and CZP 200mg injection (a total of 2 injections) at the 3 visits after the flare in order to maintain the blind to the randomized treatment.

After the loading dose (200mg Q2W or 400mg Q2W), all escaped subjects will continue full-dose CZP treatment in an open-label fashion.

The definition of flare is provided in Section 3.

At the Investigator's discretion, the subject may be withdrawn from the study at any time (eg, to receive alternative treatment for the disease).

7 STUDY TREATMENT(S)

7.1 Description of investigational medicinal product(s)

Investigational medicinal products will be supplied under the responsibility of the UCB Clinical Supply Unit. The frequency at which the 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 IXRS.

Drug supplies will consist of the following:

Certolizumab pegol is supplied as a sterile, clear, and 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 administration. 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

Part A

A Pharmacy Manual will be provided to each site containing instructions regarding drug preparation and dosing. The administration schedule is described in Section 5.1.1.

Study medication will be given sc by dedicated and adequately trained site personnel or the subject may start self-administering from Week 6 after training at Week 2 and Week 4.

Suitable areas for administrations are the lateral abdominal wall and upper outer thigh. During each dosing visit, if 2 injections are being administered (ie, loading dose CZP 400mg as 2 injections of 200mg each) each of the 2 injections should be administered at a separate injection site.

Study medication should be administered with a minimum of 10 days between the CZP 200mg Q2W administrations. Each deviation less than the minimum timeframe must be discussed immediately with the Medical Monitor for safety purposes.

Part B

A Pharmacy Manual will be provided to each site containing instructions regarding drug preparation and dosing. The administration schedule is described in Section 5.1.2.

Injections will be given sc by dedicated, unblinded and adequately trained site personnel. Suitable areas for administrations are the lateral abdominal wall and upper outer thigh.

Injections should be administered with a minimum of 10 days between the CZP 200mg Q2W administrations. Each deviation less than the minimum timeframe must be discussed immediately with the Medical Monitor for safety purposes.

7.3 Packaging

For Part A and B, CZP and placebo are packaged and labeled according to Good Manufacturing Practice 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 Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be adapted to the size of IMP package, and translated into the local language. Details on the labeling of the IMP 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.

Appropriate storage conditions must be ensured by a controlled temperature and by completing a temperature log in accordance with local requirements on a regular basis (eg, once a week) showing minimum and maximum temperatures reached over the recorded time interval.

In case an out of range temperature is noted, it must be immediately communicated to the Sponsor's 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 on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the Sponsor or designee 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.

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.

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 package. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

All study medication 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 study drug. 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 48 to Week 96.

7.7 Procedures for monitoring subject compliance

At each visit after IMP is dispensed, subjects must return all unused IMP and empty IMP containers. Drug accountability must be done in the subject's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

Part A (Open-Label Period: Week 0 [Baseline] to Week 48)

If a subject is found to be persistently noncompliant (3 or more missed doses in total over 48 weeks), the Sponsor, in conjunction with the Investigator, will make a decision as to whether the subject should be withdrawn from 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.

Part B (Double-Blind Period: Week 48 to Week 96)

If a subject is found to be persistently noncompliant (3 or more missed doses over any period of 48 weeks), the Sponsor, in conjunction with the Investigator, will make a decision as to whether the subject should be withdrawn from 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, nutraceutical products, 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 eCRF. This record should include the name of the drug, the dose, the date(s) of administration, and the indication for use.

7.8.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications/treatments are permitted during the study, from Baseline onward, with restrictions as specified:

- NSAIDs/cyclooxygenase 2 (COX-2) inhibitors: doses should be stable throughout the study and ad hoc as needed (prn) inhibitors should not be used 24 hours prior to any post-Screening study visit. No change in dose or dose regimen is allowed during the study except for reasons of safety, where the NSAIDs/COX-2 inhibitors dose may be decreased or discontinued. NSAID dose may be down-titrated at Investigator discretion. The reduction in NSAID dose if clinically indicated is permitted at the discretion of the Investigator until Week 28, however after that timepoint the NSAID treatment should remain stable as much as possible.
- Stable doses of analgesics (including, but not limited to acetaminophen, paracetamol, NSAIDs, opiates or combinations) will be permitted except that ad hoc (prn) usage is prohibited within the 14 days prior to Baseline or 24 hours prior to any post-Screening assessments.
- Corticosteroids (see Section 7.8.2 for prohibited corticosteroids):
  - Oral chronic stable doses are allowed as long as the maximum daily total prednisone equivalent dose is ≤10mg. Oral corticosteroid tapers of less than 14 days used to treat other indications (asthma exacerbation, contact dermatitis, etc.) are allowed as long the maximum daily dose is ≤20mg. The taper must end 1 week before a study visit.
  - Intra-articular (ia): ia administrations of corticosteroids are permissible in peripheral joints; however, after an ia injection the joint will no longer be evaluated for data regarding swollen and tender joints.
  - Intravenous (iv): iv administration of corticosteroid will be permitted for the purposes of stress dosing for a surgical procedure under general or spinal anesthesia. Furthermore, iv administration of corticosteroids 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, Week 48, or Week 96, 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.
- Slow-acting anti-rheumatic drugs (SAARDs) (only SSZ and/or HCQ and/or MTX and/or azathioprine [AZA] and/or leflunomide [LFN]: maximum SSZ ≤3g daily; HCQ ≤400mg daily; MTX ≤25mg weekly; AZA ≤150mg daily; LFN ≤20mg daily) are allowed. No change in dose or dose regimen is allowed during the study except for reasons of intolerance, where the SAARDs dose may be reduced or discontinued. No change is permitted in the route of administration for MTX (sc, or oral) during the study.

- Osteoporosis medications (eg, risedronate, alendronate, ibandronate, denosumab, cathepsin K inhibitor, cinacalcet, calcitonin) with the exception of iv bisphosphonates are allowed without restriction.

7.8.2 Prohibited concomitant 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 oral, iv/ia) are permitted only as described in Section 7.8.1. Intramuscular corticosteroids and SIJ ia corticosteroid injections are not permitted.
- Hyaluronic acid may be used as ia injection in the knee only.
- Specific SAARDs (cyclosporine, cyclophosphamide, mycophenolic acid, apremilast).
- Biologicals (TNF antagonists: IFX, ADA, ETN, GOL; abatacept [ABA]; CZP; Rituximab or other anti-CD20 antibodies; tocilizumab; ustekimumab; tofacitinib; also any other biological response modifiers which are not licensed for the treatment of AS or axSpA).
- All iv bisphosphonates (zoledronic acid, ibandronate, pamidronate) are excluded.

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

If the subject requires any of the medications specified in this section, the subject must be withdrawn from the study prior to the initiation of these medications.

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

7.8.3 Rescue medication

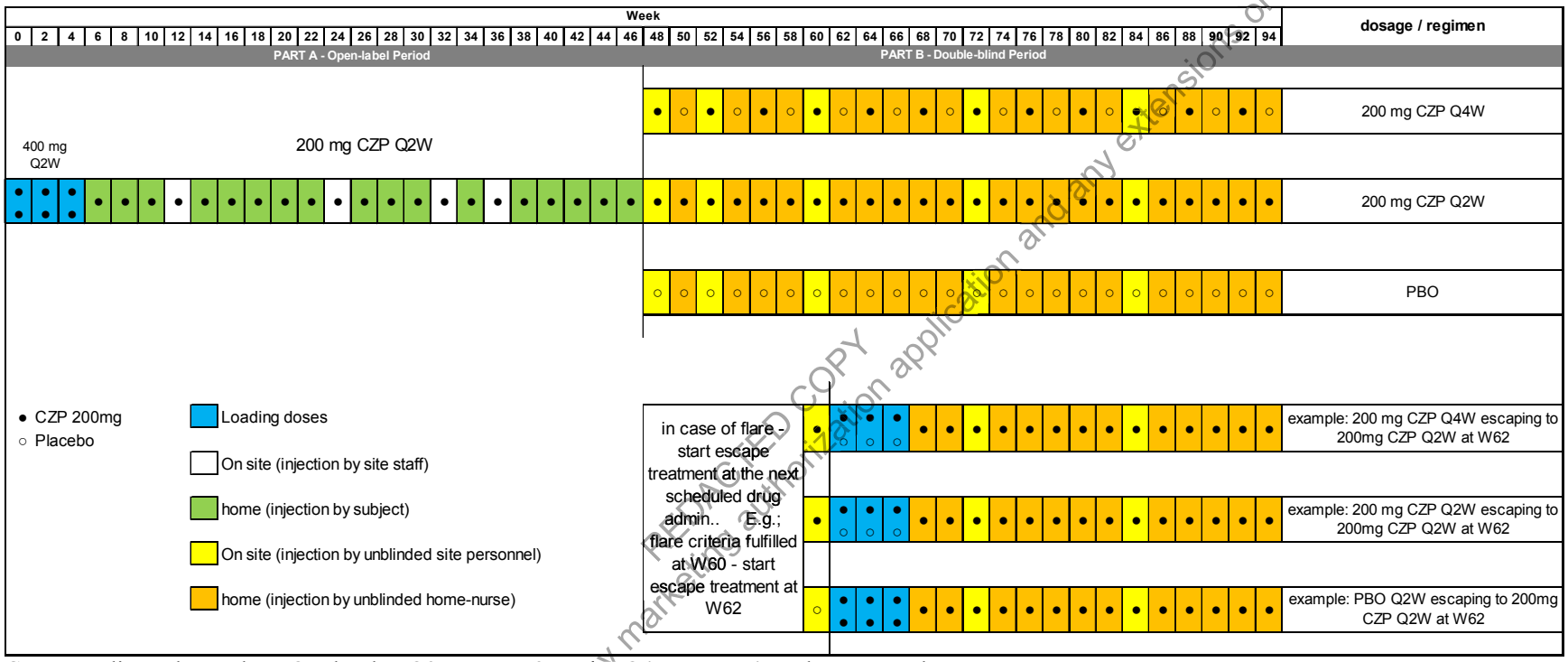
Escape treatment is as described in Section 5.1.3.

7.9 Blinding

Due to differences in presentation and viscosity between active and placebo, special precautions will be taken in order to ensure blinding of the study during Part B. The subject will receive the IMP throughout the study duration for each single administration in a sealed box with a 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 of the study (CZP 200mg or placebo). Administration of the IMP will be done according to the schedule of study assessments (Table 5.1) either onsite by appropriately trained unblinded study personnel or at home by the unblinded home nurse.

The injection schedule can be seen in Figure 7.1.

Figure 7.1: Injection Schedule



CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; W=Week

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Maintenance of study treatment blind

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

Part B of the study will be double blind and placebo controlled for 48 weeks. No study team member involved in the clinical conduct will have access to the randomization schedule until after database lock and unblinding.

7.9.1.2 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 who monitor unblinded pharmacy documentation
- Sponsor pharmacovigilance staff reporting serious adverse events (SAEs) to regulatory authorities
- Emergency service provider staff at the 24/7 SAE reporting hotline
- Laboratory staff analyzing blood samples for CZP plasma concentrations and ADAb
- Site study medication 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 to which treatment arm and dose the subject has been allocated by contacting 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) or designee 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 eCRF page.

7.10 Randomization and numbering of subjects

An IXRS will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by the CRO. The IXRS will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

To enroll a subject (Screening), the Investigator or designee will contact the IXRS and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the Investigator or designee and the IXRS regarding a particular subject. Subject numbers and kit numbers will be tracked via the IXRS.

The stratification for mNY classification will have the following 2 levels:

- mNY-positive
- mNY-negative

For enrollment in Part A, the IXRS will be designed to ensure that at least 45% and no more than 55% of the subjects belong to each of the 2 clinical subgroups above. Throughout the study, IXRS will be used for the calculation of ASDAS.

To randomize a subject (Week 48), the Investigator or designee will contact the IXRS and provide brief details about the subject to be randomized. The IXRS will automatically inform the Investigator or designee of the subject's randomization number. The IXRS will allocate kit numbers to the subject based on the subject number during the course of the study.

Randomization will be stratified on:

- Geographic region (North America, Western Europe, Eastern Europe, and Asia)
- mNY classification

In order to eventually end up with 210 subjects in sustained clinical remission qualifying for Part B, the enrollment will be adjusted accordingly. For such, the ASDAS will be monitored during Part A at various timepoints to predict the expected percentage of enrolled subjects responding well to the treatment and likely to achieve sustained remission at the end of Part A.

Subjects will be allocated to treatment during Part B in a 1:1:1 ratio (CZP 200mg Q2W: CZP 200mg Q4W: placebo).

8 STUDY PROCEDURES BY VISIT

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

During the study, the Investigator will assess each subject over the entire study period of up to 109 weeks including a SFU Period of 10 weeks after the last dose. Visit windows of ±3 days on either side of the scheduled dosing are permitted; however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±3 days is relative to Baseline and 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. For the conduct of MRI, the acceptable time window is ±2 weeks.

8.1 Screening Visit (up to 5 weeks)

Prior to any study activities, subjects will be asked to read and sign an informed consent form for participation in the study AS0005 and - optional - for obtaining pharmacogenomic samples. All informed consent forms have been approved by an IEC/IRB and the Sponsor and comply 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 procedure, 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:

- Review inclusion/exclusion criteria
- Confirm informed consent
- Demographic data (includes date of birth, gender, race/ethnicity)
- Washout of prohibited medications
- Significant past medical and procedure history and concomitant disease (includes allergy and any current symptoms); axSpA history; history of extra-articular manifestations (including number of extraarticular episodes during the previous 12 months for psoriasis and IBD and 24 months for uveitis before Screening)
- Vital signs (pulse rate, systolic and diastolic blood pressures, temperature and respiratory rates)
- Hematology, biochemistry, and urine for clinical laboratory values (includes a serum pregnancy test for women of childbearing potential, HLA-B27 and testing to rule out hepatitis B surface antigen, antibodies to hepatitis C, antibodies to HIV, and CRP)
- Physical examination (including weight, evaluation of signs and symptoms of active TB and risk factors for exposure to TB)
- Screening chest x-ray must have occurred within 3 months prior to Screening
- TB test: IGRA test (QuantiFERON TB GOLD test [or another WHO-validated IGRA test such as Elispot test only when QuantiFERON test indicated but not available]).
- TB evaluation questionnaire

- Sacroiliac joint x-ray (centrally read). An SIJ x-ray performed ≤12 months prior to the Baseline Visit maybe used as the Baseline assessment provided that the film can be submitted and meets the requirements for central reading.
- MRI (centrally read)
- BASMI and Spinal mobility assessments
- BASDAI
- PtGADA
- Prior medications
- Fecal sample kit provided to the subject
- Contact the IXRS to indicate the subject has been screened

The period between the Screening and Baseline Visits must not exceed 5 weeks. The Screening chest x-ray should be read by a radiologist or 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 retesting of CRP is permitted during the Screening Period in order to meet the Inclusion Criteria.

Subjects who initiate treatment for LTB infection during the Screening Period must repeat initial screening laboratory parameters, all examinations, and questionnaires (after receiving at least 4 weeks of treatment for LTB infection) prior to randomization in the study, and must plan to continue the full course of therapy. It is recommended that the QuantiFERON TB GOLD test be the first test performed at Screening to reduce the number of screening procedures conducted for any QuantiFERON positive subjects that may need to be treated for TB prophylaxis or potentially withdrawn from the study. The Investigator must assess that the subject's likelihood of completing the therapy is high and duly record their opinion in the subject's record prior to randomizing the subject.

8.2 Baseline Visit (Week 0)

Subjects qualifying for this study will have the following procedures performed/recorded prior to study medication administration:

- Review of inclusion/exclusion criteria (The qualifying CRP levels from the Screening Period will be used for the inclusion criteria review at Baseline.)
- Vital signs (pulse rate, systolic and diastolic blood pressures, temperature and respiration rates)
- Blood samples will be collected for hematology, biochemistry analyses, serum calprotectin, and CRP
- Urine will be collected for urinalysis and for a urine pregnancy test for women of childbearing potential
- Physical examination (including extra-articular assessments, height, and weight)
- TB questionnaire

- 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
- PtGADA
- PhGADA
- WPS
- Resources utilization
- IBD-Q
- Plasma sample for CZP concentration, ADAb
- Plasma sample for biomarkers, if applicable
- Genetics/epigenetics, proteomics if applicable
- Stool sample provided by the subject for fecal calprotectin evaluation
- Prior medications
- 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 2 to 96/WD onsite visits

8.3.1 Weeks 2, 4, 12, 24, 32, 36, 48, 52, 60, 72, 84, and 96/WD (± 3 Days)

Assessments at these onsite visits include:

- Vital signs: pulse rate, systolic and diastolic blood pressures, temperature will be measured (all visits). If a subject experiences an AE, respiration rate will be measured in addition.
- Blood samples will be collected for hematology and biochemistry analyses (at Weeks 12, 24, 32, 36, 60, 72, 84, and at Week 96/WD), and CRP (at Weeks 2, 4, 12, 24, 32, 36, and from Week 52 onwards every 4 weeks only).
- Urine pregnancy testing for women of childbearing potential will be at Week 96/WD only.

- Urine will be collected for urinalysis (at Weeks 12, 24, 32, 36, 48, 60, 72, 84, and at Week 96/WD).
- Physical examination (at Weeks 12, 24, 36, 48, 60, 72, 84, and at Week 96/WD), including weight at Week 48 and at Week 96/WD.
- Extra-articular assessments (at Weeks 4, 12, 24, 36, 48, 52, 60, 72, 84, and at Week 96/WD).
- TB test (at Week 48 and at Week 96/WD only).
- TB questionnaire (at Weeks 12, 24, 36, 48, 60, 72, 84, and at Week 96/WD).
- MRI (at Week 48 and at Week 96/WD only).
- BASMI and spinal mobility (at Weeks 2, 4, 12, 24, 36, 48, 52, 60, 72, 84, and at Week 96/WD only).
- BASDAI (at Weeks 2, 4, 12, 24, 32, 36, 52, 60, 72, 84, and at Week 96/WD).
- BASFI (at Weeks 2, 4, 12, 24, 36, 60, 72, 84, and at Week 96/WD only).
- SF-36 (at Weeks 4, 12, 24, 36, 60, 72, 84, and at Week 96/WD only).
- ASQoL (at Weeks 2, 4, 12, 24, 36, 60, 72, 84, and at Week 96/WD only).
- EQ-5D (at Weeks 12, 24, 36, 60, 72, 84, and at Week 96/WD only).
- IBD-Q (at Week 96/WD only).
- MASES (at Weeks 12, 24, 36, 48, 60, 72, 84, and at Week 96/WD only).
- Total spinal pain NRS and nocturnal spinal pain NRS (at Weeks 2, 4, 12, 24, 36, 52, 60, 72, 84, and at Week 96/WD only).
- Swollen and tender joint counts (at Weeks 2, 4, 12, 24, 36, 48, 52, 60, 72, 84, and at Completion at Week 96/WD only).
- PtGADA (at Weeks 2, 4, 12, 24, 32, 36, and from Week 52 onwards every 4 weeks only).
- PhGADA (at Weeks 12, 24, 36, 48, 52, 60, 72, 84, and at Week 96/WD only).
- WPS (at Weeks 4, 12, 24, 36, 48, 60, 72, 84, and at Week 96/WD only).
- Resource utilization (at Weeks 12, 24, 36, 48, 60, 72, 84, and at Week 96/WD only).
- Plasma for CZP concentration and ADAb (at Weeks 4, 12, 24, 60, 72, 84, and at Week 96/WD only).
- Plasma for biomarkers (at Weeks 4, 12, 24, 60, 72, 84, and at Week 96/WD only), if applicable.
- Genomics and proteomics (at Weeks 12, 24, 72, and at Week 96/WD only), if applicable.
- Stool sample will be collected for fecal calprotectin at Week 48 and at Week 96/WD only.
- Blood sample will be collected for serum calprotectin at Week 12, Week 24, Week 72 and Week 96/WD only.
- Concomitant medication

- AEs
- Contact IXRS to obtain next kit numbers.
- Study drug administration (after all other visit assessments are completed and laboratory samples are drawn) (all visits except at Week 96/WD).
- Randomization at Week 48
- Check of sustained remission criteria (all visits except Weeks 2, 4, and Week 96/WD visit).

8.3.2 3 to 5 days prior to Week 48

- Blood samples will be collected for hematology and biochemistry analyses and CRP
- BASDAI
- BASFI
- SF-36
- ASQoL
- EQ-5D
- IBD-Q
- Total spinal pain NRS and nocturnal spinal pain NRS
- PtGADA
- Plasma for CZP concentration and ADAb
- Plasma for biomarkers
- Genetics
- Blood sample will be collected for serum calprotectin
- AEs

8.4 Weeks 6 to 94 home visits and home nurse visits

8.4.1 Home visits during Part A

Assessments at these home visits include:

- Study drug self-administration at home (at Weeks 6, 8, 10, 14, 16, 18, 20, 22, 26, 28, 30, 34, 38, 40, 42, 44, and 46)
- Subjects will be contacted by telephone in between the onsite visits (at Weeks 6 to 10, 14 to 22, 26 to 30, and 38 to 46)

8.4.2 Home and home nurse visits during Part B

Assessments at these home and nurse visits include:

- Vital signs: pulse rate, systolic and diastolic blood pressures, temperature will be measured. If a subject experiences an AE, respiration rate will be measured in addition (at Week 50, Weeks 54 to 58, 62 to 70, 74 to 82, and 86 to 94 only)

- CRP and PtGADA (at Weeks 50, 56, 64, 68, 76, 80, 88, and 92)
- BASDAI (at Weeks 50, 56, 64, 68, 76, 80, 88, and 92)
- Contact IXRS to report kit number (all Visit at Weeks 50, 54 to 58, 62 to 70, 74 to 82, and 86 to 94)
- Nurse visit at subject home including to perform study medication administration (at Weeks 50, 54, 56, 58, 62, 64, 66, 68, 70, 74, 76, 78, 80, 82, 86, 88, 90, 92, and 94)
- Check of sustained remission criteria (at Weeks 50, 56, 64, 68, 76, 80, 88, and 92)

8.5 Study procedures after flare until the final assessment visit at Week 96/WD

The assessment schedule for subjects experiencing a flare in Part B will start 2 weeks after the flare condition is fulfilled (Escape Week 0) and will end 2 weeks before the final assessment visit at Week 96 (whereas the appointment for Week 96 is to be scheduled in accordance to the regular assessment schedule [Table 5.1] with Week 0 as Baseline). If the flare occurs late in Part B (at or after Week 82), the subject must receive the escape treatment for 12 weeks (eg, starting at Week 84 [Escape Week 0] until Week 96 [Escape Week 12]). The final assessments at study end (as laid down for Week 96 of the regular schedule) must be performed 2 weeks after the last study dose administration accordingly (ie, 98 weeks after Baseline for the example provided).

Assessments and their timing after a flare are specified in Table 5.2 and include:

- Vital signs: pulse rate, systolic and diastolic blood pressures, temperature will be measured at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD. If a subject experiences an AE, respiration rate will be measured in addition
- Blood samples will be collected for hematology and biochemistry analyses at Escape Week 0 and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- Urine will be collected for urinalysis at Escape Week 0 and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- CRP at Escape Weeks 0, 2, 4, and every 4 weeks thereafter until the final assessment visit at Week 96/WD
- MRI at Escape Weeks 0 and 12, and at final assessment visit at Week 96/WD, if the last MRI was done at least 12 weeks prior to Week 96/WD
- Stool sample will be collected for fecal calprotectin and blood sample for serum calprotectin at Escape Weeks 0 and 12
- IBD-Q at Escape Weeks 0 and 12
- Physical examination at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- Extra-articular assessments at Escape Weeks 0, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD

- TB questionnaire at Escape Week 0 and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- BASMI and spinal mobility at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- BASDAI at Escape Weeks 0, 2, 4, and every 4 weeks thereafter until the final assessment visit at Week 96/WD
- BASFI at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- SF-36 at Escape Weeks 0, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- ASQoL at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- EQ-5D at Escape Weeks 0, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- MASES at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD.
- Total spinal pain NRS and nocturnal spinal pain NRS at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- PtGADA at Escape Weeks 0, 2, 4, and every 4 weeks thereafter until the final assessment visit at Week 96/WD
- PhGADA at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- WPS at Escape Weeks 0, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- Resource utilization at Escape Weeks 0, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- Plasma for CZP concentration and ADAb at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- Plasma for biomarkers at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD, if applicable.
- Concomitant medication at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- AEs
- Contact IXRS to obtain next kit numbers
- Study drug administration (after all other visit assessments are completed and laboratory samples are drawn) at site and study drug self-injection at home

Refer to Table 5.1 and Section 8.3 for the final assessments due at Week 96/WD.

8.6 Safety Follow-Up Visit

Assessments at this visit 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)
- Blood samples will be collected for hematology, biochemistry analyses, and pregnancy test
- Urine will be collected for urinalysis
- Physical examination
- Plasma for CZP concentration and ADAb
- Plasma for biomarkers
- Concomitant medication
- AEs
- Contact IXRS to indicate that subject has completed the SFU

8.7 Withdrawal Visit

Assessments to be conducted at the WD Visit are specified in Section 8.3 for Week 96/WD.

8.8 Unscheduled Visit

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 assessments may be performed dependent on the presenting reason:

- Vital signs
- Blood samples for hematology, biochemistry analyses, 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

9 ASSESSMENT OF EFFICACY

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

9.1 Assessment of primary and secondary efficacy variables

9.1.1 ASAS20, ASAS40, 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:

- Patient's Global Assessment of Disease Activity (see Section 9.2.3)

- Pain assessment (the total spinal pain NRS score)
- Function (represented by BASFI, Section 9.1.3)
- Inflammation (the mean of the BASDAI questions 5 and 6, [see Section 9.1.2] 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 PR response is defined as a score of ≤2 units on a 0 to 10 unit scale in all 4 domains listed above for ASAS20.

The ASAS variables will be calculated at Weeks 0, 2, 4, 12, 24, 36, 48, 52, 60, 72, 84, and 96.

The ASAS assessments per visit are described in the schedule of study assessments Table 5.1.

9.1.2 Bath ankylosing spondylitis disease activity index (BASDAI)

The most common instrument used to measure the disease activity of AS from the subject's perspective and in the broad AxSpA population is the BASDAI (van Tubergen et al, in press 2015; 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. The final BASDAI score ranges from 0 to 10, with lower scores indicating lower disease activity. The minimal clinically important difference (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.

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

The BASDAI is calculated as follows:

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

Fatigue item of the BASDAI

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

The BASDAI assessments per visit are described in the schedule of study assessments Table 5.1.

9.1.3 Bath ankylosing spondylitis functional index (BASFI)

The BASFI is a validated disease-specific instrument for assessing physical function (van Tubergen et al, in press 2015; Calin et al, 1994, van der Heijde et al, 2005). 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, 2002a). The BASFI is the mean of the 10 scores such that the total score ranges from 0 to10, with lower scores indicating better physical function. The MCID used to interpret scores is 7mm on a 0 to 100mm VAS or 17.5% of the Baseline score (Pavy et al, 2005); an MCID of 1 unit will be used for the NRS version.

The BASFI assessments per visit are described in the schedule of study assessments Table 5.1.

9.1.4 MRI assessments

Magnetic resonance imaging of the spine and sacroiliac joints will be performed at Screening, Week 48, Week 96, or WD Visit if MRI was performed more than 12 weeks prior to WD. Magnetic resonance imaging 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. In addition, a single reader assessment will be performed for change from Baseline (Week 48) evaluation in sacroiliac SPARCC and ASspIMRI-a in the Berlin-modification scores for all subjects that entered Part A.

According to the ASAS/OMERACT definition, the presence of bone marrow oedema (BMO) or osteitis is highly suggestive of SpA that is located in the typical anatomical areas (subchodral or periarticular bone marrow). There must be either more than 1 BMO lesion on 1 slice or a lesion that is present on at least 2 consecutive slices (Rudwaleit et al, 2009b). The ASAS/OMERACT definition will be used for the classification of all Screening MRIs by the central readers. In practice, this is very similar to the SPARCC SIJ ≥2 definition of MRI which requires at least 2 BMO lesions to be present. A recent paper showed that the sensitivity and specificity of the ASAS/OMERACT and SPARCC SIJ score ≥2 definitions of MRI positive were identical (sensitivity 0.80, specificity 0.76) (Weber et al, 2014). For the evaluation of the inflammatory changes over time, the SPARCC SIJ definition will be applied for all MRI images.

The SPARCC scoring method for lesions found on the MRI is based on an abnormal increased signal on the short-tau-inversion recovery (STIR) sequence, representing BMO (defined as an increased signal in bone marrow on a T2-weighted sequence, reflecting an increased concentration of "free water" related to a bone lesion). Total SIJ SPARCC scores can range from 0 to 72.

In addition to the method mentioned above, MRIs may be evaluated using other reading criteria.

9.1.5 Bath ankylosing spondylitis metrology index

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 the schedule of study assessments Table 5.1.

9.1.6 Total and nocturnal spinal pain NRS

The pain in the spine due to AS (ie, "How much pain of your spine due to spondylitis do you have?"); and 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).

The pain NRS assessments per visit are described in the schedule of study assessments Table 5.1.

9.1.7 Ankylosing spondylitis disease activity score (ASDAS)

The Ankylosing spondylitis disease activity score 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 × Back pain (BASDAI Q2 result, see Section 9.1.2)

0.058 × Duration of morning stiffness (BASDAI Q6 result)

0.110 × PtGADA (see Section 9.2.3)

0.073 × Peripheral pain/swelling (BASDAI Q3 result)

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

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

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

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

The variables related to ASDAS improvement are defined as follows:

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

The ASDAS will be calculated according to the assessment schedule in Table 5.1.

9.2 Assessment of other efficacy variables

9.2.1 Ankylosing spondylitis quality of life

The ASQoL, a validated disease-specific 18-item questionnaire, has been recently developed specifically for measuring health-related quality of life (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 MCID criteria to guide the interpretation of ASQoL score changes in previous

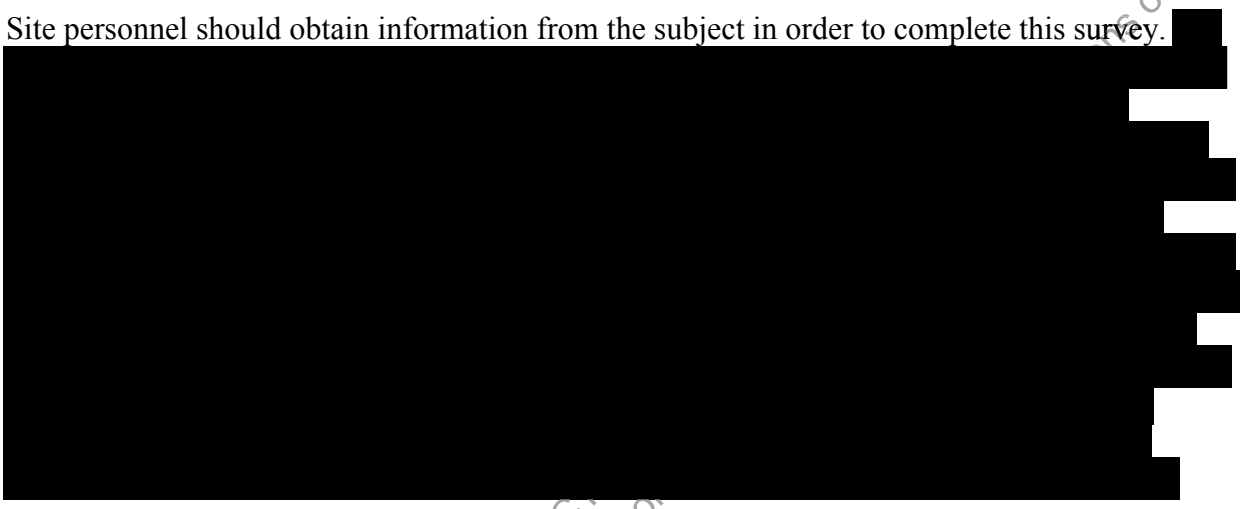
studies with a TNF-antagonist (van der Heijde et al, 2009; Davis et al, 2007). A change in ASQoL score of 2 points (ie, 10% of the total score range) will be used as the MCID to guide the interpretation of ASQoL score changes.

The ASQoL assessments per visit are described in the schedule of study assessments Table 5.1.

9.2.2 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; Osterhaus et al, 2009).

Site personnel should obtain information from the subject in order to complete this survey.



The WPS assessments per visit are described in the schedule of study assessments Table 5.1.

9.2.3 Patient's global assessment of disease activity (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, in press 2015).

The PtGADA assessments per visit are described in the schedule of study assessments Table 5.1.

9.2.4 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 2 to 4 points and 2 to 3 points, respectively (Ware et al, 2007).

The SF-36 has been used and has shown to be responsive in axSpA (van Tubergen et al, in press 2015; Haibel et al, 2008). The SF-36 will be administered per visit as described in the schedule of study assessments Table 5.1.

9.2.5 Enthesitis (MASES)

The Maastricht Ankylosing Spondylitis Enthesitis Score 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 the schedule of study assessments Table 5.1.

9.2.6 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 the schedule of study assessments Table 5.1.

Table 9.1: Swelling and tenderness grading

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

9.2.7 Physician's global assessment of disease activity

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 made without any knowledge of the PtGADA.

The PhGADA will be completed as described in the schedule of study assessments Table 5.1.

9.2.8 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 the schedule of study assessments Table 5.1.

9.2.9 Health status (EQ-5D)

The EQ-5D is comprised of a 5-item health status measures and a visual analog rating scale. 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 scored levels for 5 dimensions can be combined in a 5-digit number describing the respondent's health profile or can be converted into a single summary index. The published mean Minimally Important Difference (MID) for the index value is 0.074 (range -0.011 to 0.140) and the SRM of 0.24 (range -0.05 to 0.43) (Walters et al, 2005). The EQ-5D VAS records the respondent's self-rated health status on a vertical 20cm scale, 0 to 100 graduated (0=worst imaginable health status, 100=best imaginable health status). The MID for VAS of 7 in cancer patients was published in 2007 by Pickard et al. (Pickard et al, 2007).This instrument is to be completed by the subject as described in the schedule of study assessments Table 5.1.

9.2.10 Resource utilization

Study specific questionnaires (standard eCRF 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 (including length of stay)

Site personnel should obtain information from the subject and corroborate data with known AEs and SAEs in order to complete this survey as described in the schedule of study assessments Table 5.1. The recall period for the questionnaire will be the previous 4 weeks.

9.2.11 Extra-articular assessments

The evolution of associated nonmusculoskeletal features including IBD, psoriasis and uveitis (including their severity), and flare rate history will be assessed as described in the schedule of study assessments Table 5.1.

9.2.12 Fecal and serum calprotectin

The calgranulins, S100A8/S100A9 and S100A12, are calcium-binding proteins of the S100 family. They are released from activated monocytes and granulocytes at local sites of inflammation during the early phase of the immune response. Extracellularly, they exert important pro-inflammatory effects, thereby providing stimulation and amplification of the innate immune reaction. Calgranulins can be measured in serum and stool, and have been found to be very sensitive markers of innate immune activation. Moreover, the S100A8/S100A9 heterodimer, also called calprotectin, has been established for a long time as a fecal marker of disease activity in inflammatory bowel disease (Foell et al, 2009; Foell et al, 2007).

For all subjects, fecal and serum calprotectin will be examined for gut inflammation as described in the schedule of study assessments Table 5.1. Fecal calprotectin will be measured at Baseline, Week 48 and Week 96 and serum calprotectin will be measured at Baseline, Week 12, Week 24, 3 to 5 days prior to Week 48, Week 72, and Week 96 for the completers. For escapers, an additional sample will be collected at the time when they are escaping (Week 0) and 12 weeks thereafter.

9.2.13 Inflammatory Bowel Disease Questionnaire assessment

The Inflammatory Bowel Disease Questionnaire is a validated quality of life questionnaire, which combines an assessment of symptoms as a result of IBD, the way the subject has been feeling in general, and how their mood has been over the previous 2 weeks.

The IBD-Q (Guyatt et al, 1989) is a widely used disease-specific instrument that has been validated to be reliable and reproducible in assessing HRQoL in CD. It contains 32 questions covering 4 domains of subjects' lives (bowel symptoms, systemic symptoms, emotional function, and social function).

Subjects will be asked to answer questions relating to the impact of their CD on their HRQoL over the 2 weeks prior to their study visit using the IBD-Q. The IBD-Q must be completed by the subject prior to start any study-related activities.

Total score will be calculated for this study. An IBD-Q response is defined as a clinically meaningful improvement in the IBD-Q total score and corresponds to an increase in the IBD-Q total score ≥16 points from Baseline (Irvine, 1999). The IBD-Q remission is defined as an IBD-Q total score ≥170 points (Guyatt et al. 1989).

The IBD-Q will be completed by the subject as described in the schedule of study assessments Table 5.1.

10 ASSESSMENT OF PHARMACOKINETICS AND PHARMACOGENOMICS VARIABLE(S)

Plasma samples for the measurement of CZP concentrations will be taken at Baseline and Weeks 4, 12, 24, 3 to 5 days prior to Week 48, and Weeks 60, 72, 84, 96/WD, and at the SFU visit 10 weeks after the last dose of study medication. For escapers plasma samples will be taken after the flare at Escape Weeks 0, 2, 4, 12, and further every 12 weeks until Week 96/WD (refer to Table 5.2 for details). 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.

Plasma samples for possible analyses of exploratory biomarkers will be taken at Baseline and Weeks 4, 12, 24, 3 to 5 days prior to Weeks 48, and Weeks 60, 72, 84, 96/WD, and at the SFU visit 10 weeks after the last dose of study medication. For escapers plasma samples will be taken after the flare at Escape Weeks 0, 2, 4, 12, and further every 12 weeks until Week 96/WD (refer to Table 5.2 for details). Selected biomarkers that may be analyzed are: MMP-3; BMP-2, -4, and -7, WNT1, WISP, Gremlin, DKK1, Sclerostin, Hedgehog proteins (Shh, Ihh, Dhh), Collagen turnover/cleavage products, collagen type X, VEGF, citrullinated vimentin fragments, cytokines: IL13, IL17 A and F, IL23, IL34, TGF-β, M-CSF, GM-CSF, CSF-1, sCSF1r levels.

Blood samples will be drawn for possible genetic, genomic, and proteomic analysis at Baseline (Week 0), and for genomic and proteomics analysis only, at Weeks 12, 24, 3 to 5 days prior to Week 48, 72, and at Week 96/WD to enable exploratory evaluation of biomarkers relative to drug treatment 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 the Central Laboratory facilities for up to 20 years.

11 ASSESSMENT OF IMMUNOGENICITY VARIABLES

Plasma samples for the measurement of ADAb and potentially NAb levels will be taken at Baseline (Week 0) and Weeks 4, 12, 24, 48, 60, 72, 84, 96, and the SFU visit (10 weeks after the last dose of study medication). For escapers, plasma samples will be taken after the flare at Escape Weeks 0, 2, 4, 12, and further every 12 weeks until Week 96/WD (refer to Table 5.2 for details).

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

12 ASSESSMENT OF SAFETY

12.1 Adverse events

12.1.1 Definition of adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that 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 a

medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

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 the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial 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, diary cards) 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 eCRF 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 eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

12.1.4 Follow up of adverse events

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

If an AE is 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 and repeated AE, 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 Patient Safety (PS) 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 pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an early discontinuation visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the early discontinuation visit.
- A Safety Follow-Up Visit should be scheduled 10 weeks after the subject has discontinued her IMP (last dose of IMP).

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 in which the Investigator has to report on 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 PS 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 PS 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 PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow-up.

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

12.1.7 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the appropriate Drug Accountability forms and module of the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

12.1.8 Safety signal detection

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.

Safety data including SAEs, AEs, vital signs, laboratory results, and electrocardiogram (ECG) data (as applicable) will be periodically reviewed by UCB.

The data from all studies with the same IMP will be reviewed to detect as early as possible any new safety concerns related to the IMP so that the Investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed in the most appropriate and timely manner.

12.2 Serious adverse events

12.2.1 Definition of serious adverse event

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

- Death
- Life-threatening
  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious
  (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, or the development of drug dependency or drug abuse.)

- 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 preexisting 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 preexisting 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.)

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 SFU 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's 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 PS database without limitation of time.

12.3 Adverse events of interest

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

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

12.4 Immediate reporting of adverse events

The following AEs must be reported immediately:

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

12.5 Anticipated serious adverse events

The following list of Anticipated SAEs has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 12.2.2.

Table 12.1: Anticipated serious adverse events in population independent of drug exposure

Population	Anticipated SAE(s)
Rheumatoid arthritis [a]	Rheumatoid arthritis
Crohn's disease [a]	Crohn's disease Perianal abscess Abdominal pain
Ankylosing spondylitis	Ankylosing spondylitis
Psoriatic arthritis	Psoriatic arthritis
JIA	Juvenile arthritis

JIA=Juvenile Idiopathic Arthritis; SAE=serious adverse event; CD=Crohn's disease; RA=rheumatoid arthritis
[a] The lists of anticipated SAEs were based on the treatment-emergent SAEs with an incidence ≥0.5% in subject who participated in UCB sponsored placebo-controlled studies who received placebo (CD and RA safety pooling).

12.6 Laboratory measurements

Hematology, biochemistry, and urinalysis samples will be taken at Screening, Baseline (Week 0), Weeks 12, 24, 32, 36, 3 to 5 days prior to Week 48, and Weeks 60, 72, 84, 96/WD, and at the SFU Visit (10 weeks after the last dose). Testing for HLA-B27, hepatitis B surface antigen, and antibodies to hepatitis C and HIV will be performed at Screening. 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:

Table 12.2: Laboratory measurements

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

CRP=C reactive protein; RBC=red blood cells; WBC=white blood cells; HIV=human immunodeficiency virus; HLA=human leukocyte antigen

12.7 Other safety measurements

12.7.1 Pregnancy testing

Pregnancy testing must be carried out for women of childbearing potential and will consist of serum testing at Screening and SFU, and urine testing at Baseline and W96/WD.

12.7.2 Physical assessments

Physical examination will be performed at Screening, Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96/WD, and at the SFU Visit (10 weeks after the last dose). Physical examination findings will be recorded in the eCRF 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 questionnaire will be performed at Screening, Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, and at Week 96/WD Visit.

Weight is to be measured at Screening, Baseline, Week 48, and at Week 96/WD. Height will be measured at the Baseline Visit only.

12.7.3 Assessment and management of TB and TB risk factors

As TNF antagonists are known to be associated with significant risk of reactivation of LTB, appropriate rigorous precautions are being taken within the protocol (see Section 6.2 [Exclusion Criterion 16]) and Section 6.3.1 [Withdrawal Criterion 7]).

Signs and Symptoms

The Investigator should consider all potential sites of infection when assessing for TB during the physical examination, and other evaluations, and based on the subject's history. 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 with which 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.

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

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

Test Conversion

Tuberculosis test conversion is defined as a positive result (IGRA) for the current test but previous test results were negative (IGRA). All subjects with TB test conversion must immediately stop study drug administration. In case of a TB test conversion, the subject must be considered as having either a suspected new latent or an active TB infection and be promptly referred to an appropriate specialist (ie, pulmonologist, infectious disease specialist) 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, active TB infection, or non-TB mycobacterial 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, 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.

In case no prophylactic treatment is initiated, the subject has to be withdrawn.

Every action should be discussed in advance with the Medical Monitor. Latent TB is an Adverse Event of special interest (AESI) and must be reported as such.

Active TB/nontuberculosis mycobacterium

Subjects who develop active TB or nontuberculosis mycobacterium (NTMB) infection during the study (conversion demonstrated by IGRA) must be withdrawn from the study. The subject must be immediately discontinued from study medication and a WD Visit must be scheduled as soon as possible, but no later than the next scheduled visit. The subject should be encouraged to keep the SFU Visit as specified by the protocol. The TB must be documented as an SAE. Treatment should be immediately started.

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 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 96/WD Visit, complete all WD assessments, and complete an SFU Visit (10 weeks after the last dose of study medication).

12.7.3.1 Tuberculosis assessments

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB GOLD In Tube test or Elispot, if QuantiFERON TB GOLD In Tube test is not available locally), should be repeated at Week 48 and Week 96/WD for all subjects. The test results will be reported as positive, negative, or indeterminate and must be reviewed by an experienced TB specialist, radiologist, or a pulmonologist. If the assessment by IGRA is positive or indeterminate on retest for subjects who were previously negative at Screening and not treated for LTB, the subject may not continue study treatment without further evaluation by a TB specialist, prophylactic TB-treatment, and discussion with the Medical Monitor, if LTB infection is identified. If active TB is identified, subject must undergo appropriate study-specified withdrawal procedures. The retest during Screening must be done during the protocol-defined Screening window.

12.7.3.2 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 medication administration. The chest x-ray should be repeated 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 examination or on chest x-ray must be documented in the source documents and eCRF as an AE.

12.7.3.3 Tuberculosis questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will be completed at Screening, Baseline, and every 12 weeks thereafter until Week 96/WD. 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 LTB or active TB infection.

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

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

12.7.3.4 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 the subject's IGRA test converting to positive or indeterminate (and confirmed indeterminate on repeat), or the subject's questionnaire history or physical examination indicating 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 medication no earlier than 4 weeks after the start of an appropriate prophylactic therapy.

Any presumptive diagnosis or diagnosis of a TB infection (latent or active TB) is a reportable AESI. Confirmed active TB must be reported as a SAE, confirmed LTB as AESI (please see Section 12.2 and 12.3). The Investigator is to complete and submit the TB follow-up form provided.

The subject should be transferred to the care of their 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 WD Visit as soon as possible but no later than the next scheduled study visit and complete all WD Visit assessments.

The subject should be encouraged to complete an SFU Visit 10 weeks after the last dose of study medication.

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.

12.7.4 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 onsite visits including the SFU Visit (10 weeks after the last dose of study medication) with the exception of Visit 1. Respiration rate will be measured at Screening and Baseline only; and in addition at subsequent visits, if a subject experiences an AE.

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 Adherence to protocol

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

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

13.2 Monitoring

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

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

The Investigator will allow UCB (or designee) to periodically review all eCRFs 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 eCRFs, ensure that all protocol requirements, applicable authorities' regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

13.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies of eCRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

The following data will be recorded directly in the ePRO tablet and will not appear in a source document as defined above:

- Patient Reported Outcome questionnaires: SF-36, EQ-5D, PtGADA, BASDAI, BASFI, ASQoL, IBD-Questionnaire, Work Productivity Survey, 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 facilitate the process for enabling 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, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 13.2.1.

13.3 Data handling

13.3.1 Case report form completion

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

This study will also use an electronic device (Site Tablet) to capture patient reported outcomes (see Section 13.3.2).

Serious adverse event reporting will be done using the SAE form (see Section 12.2.2) 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.

13.3.2 Electronic reporting outcome

Compared to the paper subject 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 improved subject symptom and compliance. The electronic patient reported outcome (ePRO) possibilities will be used in this study.

This study will use an electronic Site Tablet having a large screen and intuitive fingertip data entry to ensure all questionnaire data are captured appropriately, completely, and on time. Only subjects' data will be collected with the tablets. Physicians' data (joint counts and PhGADA) will be entered in the eCRF or collected on worksheets.

Access to the system 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 ePRO device.

13.3.3 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management 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. This study is performed using RDC; the data are entered into the eCRFs once and are subsequently verified.

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

13.3.4 Subject screening and enrollment log/subject identification code list

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

The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject.

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.

13.4 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 should also 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 IMP 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.

13.5 Archiving and data retention

The Investigator will maintain adequate records for the study, including eCRFs, 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 IMP. 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.

13.6 Audit and inspection

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

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

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

13.7 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 Statistical Analysis Plan (SAP).

14.1 Definition of analysis sets

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

The Open-Label Set (OLS) will consist of all subjects who receive at least 1 dose of study medication in the Open-Label Period of the study (Part A).

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

The Flared Set (FS) will consist of all subjects from the RS who experience a flare in Part B.

The Part B Full-Dose Set (FDS) will include all subjects from the RS who ever received a dose of CZP Q2W during Part B (including escape treatment).

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

The Safety Set Part B (SSB) will consist of all subjects in the RS who have received at least 1 dose of study medication in the Double-Blind Period of the study (Part B).

The Full Analysis Set (FAS) will consist of all subjects in the RS who have received at least 1 dose of study medication in Part B, and have valid ASDAS measurements at Week 48 and at least 1 timepoint following Week 48.

The Per Protocol Set (PPS) will be used to evaluate the sensitivity of the results of the primary efficacy analysis, which is based only on subjects who enter Part B. As such, the PPS will consist of subjects in the FAS without any major protocol deviations that may influence the validity of the data for the primary efficacy variable. Important protocol deviations will be defined and evaluated prior to unblinding.

The Pharmacokinetic Set A (PKSA) will consist of all subjects from the OLS who provide at least 1 PK sample during Part A.

The Pharmacokinetic Set B (PKSB) will consist of all subjects from the SSB who provide at least 1 PK sample during Part B.

14.2 General statistical considerations

All efficacy analyses for Part B will be performed using the RS. The FAS and PPS will be used for a sensitivity analysis on the primary endpoint only. Efficacy summaries for variables collected in Part A will be based on the OLS.

Summaries at the Week 48 timepoint for laboratory data and data collected via electronic device (Site Tablet) will be based on the assessments conducted 3 to 5 days prior to the Week 48 clinic visit.

The statistical analysis of the primary efficacy variable will account for the testing of multiple doses by using a fixed sequence testing procedure. The proportion of subjects who do not experience a flare (where flare is defined as ASDAS ≥2.1 on 2 consecutive visits or ASDAS >3.5 at any visit) will be compared between each CZP dose and placebo. The predefined order of

hypotheses testing, each at a 2-sided 0.05 significance level for the comparison between the given CZP dose and placebo, will be performed in the sequence shown below:

1. CZP 200mg Q2W vs placebo
2. CZP 200mg Q4W vs placebo

The second test will be performed irrespective of whether the first test is significant at the 0.05 level or not. However, the second test will be interpreted as statistically significant only if the first test is significant at the 0.05 level as well.

14.3 Planned efficacy analyses

14.3.1 Analysis of the primary efficacy variable

The primary efficacy variable is the proportion of subjects who do not experience a flare. The primary analysis will be based on logistic regression. The odds ratio based on the proportion of subjects who do not experience a flare will be estimated and tested between treatment groups using a logistic regression model with factors of treatment group, geographic region, and mNY criteria (yes/no). Geographic region and mNY classification are also randomization stratification factors. 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 pre-defined in the IXRS and in the SAP. Each CZP dose will be compared against placebo to establish superiority over placebo and will be tested sequentially at an alpha of 0.05 as outlined in Section 14.2.

An approach based on the principles of nonresponse imputation (NRI) will be used to impute missing values. Specifically, if a subject withdraws from Part B at any point, they will be considered as having not responded to treatment. Therefore, they will be assumed to have experienced a flare during Part B for analysis purposes. If a subject has an intermittent missing ASDAS score (ie, a missing value at 1 visit but nonmissing values at the previous and subsequent visit), then the missing value will be ignored and flare will be based on the 2 available values. If the ASDAS score is missing at 2 or more consecutive visits, then the subject will be treated as having experienced a flare (even if ASDAS scores are available after the missed visits).

Subgroup analyses based on age, gender, race, region, CRP level, ADAb status, and mNY criteria will be performed. These analyses will be done for the primary efficacy variable and will be based on descriptive statistics only.

14.3.2 Analysis of the secondary efficacy variables

14.3.2.1 Part A analysis

The secondary efficacy variables defined in Part A are as follows:

- Percentage of subjects achieving sustained remission at Week 48
- ASDAS disease activity (ASDAS-ID and ASDAS-MD, ASDAS-HD, ASDAS-vHD) at Week 48
- ASDAS clinical improvement (ASDAS-MI and ASDAS-CII) at Week 48

The percentage of subjects achieving sustained remission, ASDAS-MI, and ASDAS-CII at Week 48 will be summarized using descriptive statistics (counts and percentages). Separate summaries will be done using NRI and observed case data.

Ankylosing Spondylitis Disease Activity Score disease activity at Week 48 will also be summarized using descriptive statistics, where counts and percentages are reported for each of the 4 categories. Two summaries will be provided: One will derive disease activity at Week 48 using last observation carried forward (LOCF, impute using the last post-Baseline nonmissing result) for missing values and the other will be based on observed case data.

All summaries of secondary efficacy variables in Part A will be based on the OLS.

14.3.2.2 Part B analysis

The time to flare will be analyzed using Kaplan-Meier methods. For those who meet the criteria for flare, the time will be defined as the length in days from randomization in Part B until the visit at which the criteria for flare were met. Subjects who discontinue the study without meeting the criteria for flare will be censored at the time of their last study visit. Subjects who complete the study without meeting the criteria for flare will be censored at their Week 96 visit. Between group differences will be analyzed with the log-rank statistic.

The changes from Baseline in ASDAS, BASDAI, BASFI, and BASMI at Week 96 for the RS will be compared between treatment groups using a mixed model for repeated measures (MMRM). The pattern of missingness for these variables is assumed to be missing at random (MAR). Subjects who enter Part B will have already demonstrated sustained remission through 48 weeks on CZP 200mg Q2W. Many of these subjects will be randomized to receive placebo and will, therefore, be more likely to experience a flare. Postflare data for subjects who experience a flare (in any treatment group) will be treated as missing for the MMRM analysis. It is further assumed that most subjects who discontinue at this late stage in the study (ie, during Part B) will do so as a result of reduced efficacy. Therefore, missing efficacy data due to either flare or study treatment discontinuation should be dependent on the observed efficacy scores, but independent of unobserved data.

The MMRM model will include Baseline score as a fixed-effect covariate, treatment group, region, mNY criteria (yes/no), and visit as fixed-effect categorical factors, and Baseline-by-visit and treatment group-by-visit as interaction terms. An unstructured correlation pattern will be used to estimate the variance-covariance of the within-subject repeated measures. Tables will present the adjusted means for placebo and the CZP doses (200mg Q2W and 200mg Q4W), the respective difference to placebo, the corresponding p-value, and 95% CI.

Change from Baseline in SIJ SPARCC and spine ASspIMRI-a in the Berlin modification scores at Week 96 will be compared between treatment groups using analysis of covariance (ANCOVA) for observed values only (ie, no imputation). The model will include Baseline score, treatment group, region, and mNY criteria (yes/no). Tables will present the adjusted means for placebo and the CZP doses (200mg Q2W and 200mg Q4W), the respective difference to placebo, the corresponding p-value, and 95% CI.

The binary secondary efficacy variables (ASDAS-MI, ASDAS-CII, ASAS20, ASAS40, ASAS5/6, ASAS PR, and BASDAI50 response) at Week 96 will be analyzed using a logistic regression. The odds ratio of the responder rates at Week 96 will be estimated and tested

between treatment groups using a logistic regression model with factors of treatment group, region, and mNY criteria (yes/no). Tables will present the responder rates for placebo, CZP 200mg Q2W, and CZP 200mg Q4W, the respective effect estimates (adjusted odds ratio with reference to placebo), p-values, and 95% CIs. Subjects with a missing responder status at Week 96 will be treated as a nonresponder for analysis purposes (ie, NRI).

Ankylosing Spondylitis Disease Activity Scores (ASDAS-ID, ASDAS-MD, ASDAS-HD, ASDAS-vHD) will be summarized by treatment group using summary statistics (counts and percentages) based on observed case data.

In addition to the analyses mentioned above, descriptive statistics (number of available observations [n], mean, median, SD, minimum, and maximum) will be provided by treatment group for the secondary efficacy variables. The descriptive analyses will be covered in the tables summarizing the variables over time. This will include a summary of the actual values, change from Baseline (Week 0), and change from randomization Baseline (Week 48). The statistical comparisons described for secondary efficacy variables 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. All analyses and summaries of secondary efficacy variables in Part B will be based on the RS.

14.3.2.3 Part B analysis for subjects who experience a flare

For subjects who experience a flare during Part B, the secondary efficacy variables listed below will be analyzed. The timepoint for these secondary efficacy analyses will be at Escape Week 12).

- ASDAS disease activity (ASDAS-ID, ASDAS-MD, ASDAS-HD, and ASDAS-vHD)
- ASDAS clinical improvement (ASDAS-CII, ASDAS-MI)
- ASAS20, ASAS40, ASAS5/6, and ASAS PR response
- Change from Baseline in ASDAS, BASDAI, BASFI, and BASMI
- Change from Baseline in MRI

These variables will be summarized by treatment group using descriptive statistics. For the binary response variables (ASDAS-CII, ASDAS-MI, ASAS20, ASAS40, ASAS5/6, and ASAS PR), counts and percentages at Escape Week 12 visit will be displayed. For comparative purposes, the tables will also include the responder counts and percentages at the visit where flare criteria were met. ASDAS disease activity will be summarized in a similar way based on the 4 categories.

For the continuous variables (ASDAS, BASDAI, BASFI, BASMI), quantitative descriptive statistics by treatment group will be displayed. This summary will include the actual results at Escape Week 12, change from Baseline (Week 0), change from randomization Baseline (Week 48), and change from the visit in which the flare occurred.

All Part B summaries after subjects experience a flare will be based on observed case data and will use the FS.

14.3.3 Other efficacy analyses

14.3.3.1 Part A

The other efficacy variables for Part A as outlined in Section 4.1.3.1 will be summarized by visit and treatment group using descriptive statistics for the timepoint itself and for the change from Baseline. This will be done for the OLS using observed case data and with imputation using LOCF. Further details are described in the SAP.

Tables for the binary variables will display the responder rates for the various timepoints over time. This will be done for the OLS using observed case data and with imputation using NRI.

14.3.3.2 Part B

Treatment group comparisons for both CZP groups 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 with variables of Baseline score, treatment group, region, and mNY criteria (yes/no) in the model. The treatment differences and corresponding 95% CIs will be calculated based on the adjusted means. Missing values will be imputed using LOCF. This analysis approach will be used for the following variables:

- Total spinal pain
- Nocturnal spinal pain
- PtGADA
- Morning stiffness (BASDAI 5 and 6)
- SF-36 PCS, MCS, and physical function domain
- Fatigue NRS
- ASQoL

Such analyses will also be done for the following continuous variables: ASDAS, BASDAI, BASFI, and BASMI will be analyzed using a MMRM similar to the one specified in Section 14.3.2.2 at timepoints not covered in the secondary efficacy analyses. Additionally, ASDAS-MI, ASDAS-CII, ASAS, and BASDAI50 response variables will be analyzed using a logistic regression model similar to the one specified for binary response variables in Section 14.3.2.2 at timepoints not covered in the 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 will also be performed for WPS scores using the nonparametric bootstrap-t method. This will be explained in greater detail in the SAP.

All other efficacy variables will be summarized descriptively by visit and treatment group using observed case and imputed data based on the RS.

14.3.3.3 Part B analysis for subjects who experience a flare

The other efficacy variables for subjects who experience a flare in Part B as outlined in Section 4.1.3.3 will be summarized by visit and randomized treatment group using descriptive

statistics for the timepoint itself and for the change from Baseline. A subset of variables will summarize the change from randomization Baseline (Week 48) and the change from the visit at which the flare occurred. This will be done for the FS using observed case data.

14.4 Planned safety and other analyses

14.4.1 Safety analyses

The frequency of all AEs by study period (Part A and Part B) will be presented separately by System Organ Class, high-level term, and preferred term and for Part B by each treatment group. 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 by 100 patient years.

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

14.4.2 Pharmacokinetic and immunogenicity 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, 95% CI, geometric coefficient of variation, arithmetic mean, arithmetic SD, median, minimum, and maximum.

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.

14.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol that could potentially have a meaningful impact on study conduct or on the primary efficacy outcomes 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 agreed upon prior to unblinding to confirm exclusion from analysis sets.

14.6 Handling of dropouts or missing data

For the primary efficacy variable (percentage of subjects in Part B who do not experience a flare), an approach based on the principles of NRI will be used to impute missing values. Specifically, if a subject withdraws from Part B at any point, they will be considered as having not responded to treatment. Therefore, they will be assumed to have experienced a flare during Part B for analysis purposes. If a subject has an intermittent missing ASDAS score (ie, a missing value at 1 visit but nonmissing values at the previous and subsequent visit), then the missing value will be ignored and flare will be based on the 2 available values. If the ASDAS score is missing at 2 or more consecutive visits, then the subject will be treated as having experienced a flare (even if ASDAS scores are available after the missed visits).

For the time to flare endpoint, the rules as described above for the primary endpoint will be applied to account for missing data when determining whether or not a subject experienced a flare. Subjects who discontinue the study without meeting the criteria for flare will be censored

at the time of their last study visit. Subjects who complete the study without meeting the criteria for flare will be censored at their Week 96 visit.

Selected continuous secondary efficacy variables will be analyzed using MMRM methods (see Section 14.3.2.2 for details). Missing data for binary response secondary efficacy variables will be handled using NRI. Secondary variables related to MRI will be analyzed based on the observed case data.

In general, other efficacy variables will be summarized as both observed case and with imputation (NRI for binary response variables and LOCF for continuous variables), unless otherwise specified. Nonresponse imputation is implemented by treating missing data for binary response variables as a nonresponse. The LOCF summaries will impute missing continuous data using the last post-Baseline nonmissing result. In the event that a subject has no post-Baseline data for a given continuous variable, no imputation will be performed.

14.7 Planned interim analysis and data monitoring

A database lock may be performed and an interim study report may be written, if required. The main focus of this interim analysis would be the efficacy and safety up to a certain treatment timepoint eg, after Week 48.

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.

14.8 Determination of sample size

It is anticipated that approximately 210 subjects will be randomized in a 1:1:1 ratio to the CZP 200mg Q2W, CZP 200mg Q4W, and placebo treatment groups. The primary efficacy analysis is based on the proportion of subjects who do not experience a flare during Part B of the study. The proportion of subjects who do not experience a flare during Part B is assumed to be 80%, 75%, and 45% for the CZP 200mg Q2W, CZP 200mg Q4W, and placebo treatment groups, respectively. Given these assumptions, a sample size of 70 subjects per group provides 98% power to detect a significant difference between the CZP 200mg Q2W dose and placebo and 94% power to detect a significant difference between the CZP 200mg Q4W dose and placebo using a 2-sided significance level of 0.05.

Given that subjects enter Part B only if they have achieved sustained remission in Part A, it is necessary to estimate the number of subjects needed to enroll in Part A. It is assumed that approximately 28% of subjects enrolled in Part A will achieve sustained remission and qualify for Part B. This means that about 750 subjects will be enrolled in Part A in order to have 210 subjects who are randomized into Part B. Subject response to treatment will be evaluated on an ongoing basis as subjects enroll in Part A, and the number of subjects enrolled will be adapted accordingly in order to achieve 210 subjects randomized to Part B.

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.

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 United States 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. An eCRF 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 Form, 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 him/her 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 axSpA

Imaging criteria	**ASAS clinical criteria for axSpA**
Sacroiliitis (MRI or radiographs [a]) plus ≥1 SpA feature	HLA-B27 plus ≥2 other SpA features
SpA features [b]	
Inflammatory back pain [c] Arthritis Enthesitis (heel) Uveitis Dactylitis	Psoriasis Crohn's disease/ulcerative colitis HLA-B27 Elevated CRP

ASAS=Assessment of SpondyloArthritis International Society; CRP=C-reactive protein; MRI=magnetic resonance imaging; HLA-B27=human leukocyte antigen B27; NSAID=nonsteroidal anti-inflammatory drug; SpA=spondyloarthritis

[a] 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.

[b] 'Family history for SpA' and 'Good response to NSAIDs' are excluded as SpA feature criteria.

[c] Inflammatory back pain according to ASAS criteria for axSpA 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 Corticosteroid equivalent doses

Table 18.1: Corticosteroid equivalent doses (with reference to prednisone 10mg dose)[a]

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

[a] Source: Meikle and Tyler, 1977

18.3 Protocol Amendment 1

Rationale for the amendment

This substantial amendment includes additional efficacy variables for subjects entering Part A and Part B of the study, as well as a completely new list of other efficacy variables for those subjects who experience a flare in Part B. For the purposes of analysis, 4 new analysis sets were defined; 2 of which will be used in the PK analysis, 1 which will be used in the efficacy analysis of subjects experiencing a flare in Part 2, and 1 which will be used to evaluate safety in subjects who ever received treatment with full-dose CZP during Part B of the study. Several clarifications were made including the timepoint for the assessment of the secondary efficacy variables for subjects who experience a flare in Part B, HLA-B27 as a Screening laboratory assessment, and the assessments to be performed 3 to 5 days prior to Week 48. Inconsistencies in the naming of Week 96 visit and assessments 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:

- Assessment of ePRO outcomes and CRP at Week 48 to be performed 3 to 5 days prior to Week 48. This was updated throughout the protocol.
- HLA-B27 removed from Baseline and included in Screening.
- The term “Investigator's AS” was changed to ‘PhGADA’.
- Anti-CZP antibody was abbreviated to ADAb throughout the document.
- Timepoint for assessment of secondary efficacy variables for subjects who experience a flare in Part B was changed from “Week 96 or a later timepoint” to “Escape Week 12”.
- The variable “spinal mobility” was added as 2 variables as follows:
  - Change from Baseline in spinal mobility, as assessed by occiput to wall distance.
  - Change from Baseline in spinal mobility as assessed by chest expansion.
- Efficacy variable total and nocturnal spinal pain has been changed to: total spinal pain (part of the ASAS) and nocturnal spinal pain has been separated from ASAS core components.
- Addition of variables to be assessed for subjects experiencing flare in Part B.
- Additional analysis sets for assessment of pharmacokinetic variables and for assessment of variables in subjects experiencing flare in Part B.
- Completion/Withdrawal Visit is now referred to as Week 96/Withdrawal Visit throughout the protocol.
- Serum calprotectin analysis was added in addition to the existing fecal calprotectin analysis and references to “calprotectin” alone were separated into “serum calprotectin” and “fecal calprotectin”.
- Correction of errors.

It is to be noted that typographical updates were made in the document, but not listed individually in the specific changes list.

Specific changes

Change #1

STUDY CONTACT INFORMATION

Name:	[redacted]
Address:	8010 Arco Corporate Drive Raleigh, NC 27617
Phone:	[redacted]
Fax:	

Has been changed to:

Name:	[redacted]
Address:	Alfred-Nobel-Strasse 10 40789 Monheim, Germany
Phone:	[redacted]
Fax:	

Change #2

STUDY CONTACT INFORMATION

Name:	[redacted]
Address:	8010 Arco Corporate Drive Raleigh, NC 27617
Phone:	[redacted]
Fax:	

Has been changed to:

Name:	[redacted]
Address:	8010 Arco Corporate Drive Raleigh, NC 27617, USA
Phone:	[redacted]
Fax:	

Change #3

The following abbreviations were added:

ADAb	anti-CZP antibody
ASAS20, 40	Assessment of SpondyloArthritis International Society 20%, 40% response criteria
FDS	Full Dose Set
FS	Flared Set
M-CSF	macrophage colony-stimulating factors
PKSA	Pharmacokinetic Set A
PKSB	Pharmacokinetic Set B

Change #4

1. SUMMARY, paragraph 1

Study AS0005 is a multicenter, open-label (Part A) followed by a randomized, double-blind, parallel-group, placebo-controlled clinical study (Part B) to evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of certolizumab pegol (CZP) in adult subjects with active axial spondyloarthritis (axSpA) in sustained remission who continued either on full-dose treatment (CZP 200mg every 2 weeks [Q2W]), on a dose reduction (CZP 200mg every 4 weeks [Q4W]) or withdrawal of CZP treatment. The study includes 2 parts an Open-Label Run-In Period for 48 weeks (Part A) followed by a Double-Blind Period for 48 weeks (Part B) with 3 treatment arms (200mg CZP Q2W [referred to as full-dose], 200mg CZP Q4W [referred to as half-dose], and placebo), and a Safety Follow-Up (SFU) Period for 10 weeks after the last dose of study medication.

Has been changed to:

Study AS0005 is a multicenter, open-label (Part A) followed by a randomized, double-blind, parallel-group, placebo-controlled clinical study (Part B) to evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of certolizumab pegol (CZP) in adult subjects with active axial spondyloarthritis (axSpA) in sustained remission who continued either on full-dose treatment (CZP 200mg every 2 weeks [Q2W]), on a dose reduction (CZP 200mg every 4 weeks [Q4W]) or withdrawal of CZP treatment (placebo). The study includes: an Open-Label Run-In Period of 48 weeks (Part A) followed by a Double-Blind Period of 48 weeks (Part B) with 3 treatment arms (200mg CZP Q2W [referred to as full-dose], 200mg CZP Q4W [referred to as half-dose], and placebo), and a Safety Follow-Up (SFU) Period for 10 weeks after the last dose of study medication.

Change #5

1. SUMMARY, paragraphs 8, 9, and 10

The following are secondary efficacy variables for subjects who experience a flare in Part B. These will be evaluated at Week 96 or a later timepoint, if applicable: 1) ASDAS disease activity and clinical improvement, 2) ASAS20, ASAS40, ASAS5/6, and ASAS PR response, and 3) Change from Baseline in ASDAS, BASDAI, BASFI, BASMI, and MRI.

Further, other efficacy variables for Part A, and Part B are listed in Section 4.1.3.1 and Section 4.1.3.2, respectively.

Pharmacokinetic and pharmacogenomic variables are listed in Section 4.1.3.3, and immunological variables are listed in Section 4.3.

Has been changed to:

The following are secondary efficacy variables for subjects who experience a flare in Part B. These will be evaluated at Escape Week 12: 1) ASDAS disease activity and clinical improvement, 2) ASAS20, ASAS40, ASAS5/6, and ASAS PR response, and 3) change from Baseline in ASDAS, BASDAI, BASFI, BASMI, and 4) change from Baseline in sacroiliac SPARCC and ASspIMRI-a in the Berlin modification scores.

Further, other efficacy variables for Part A, and Part B and for subjects who experience a flare in Part B are listed in Section 4.1.3.1, Section 4.1.3.2, and Section 4.1.3.3, respectively.

Pharmacokinetic and pharmacogenomic variables are listed in Section 4.2 and immunological variables are listed in Section 4.3.

Change #6

2.5. RATIONALE, paragraph 4

For axSpA patients suffering from gut inflammation, the QoL will be assessed with an inflammatory bowel disease questionnaire (IBD-Q) and, in addition to this, an analysis of calprotectin in stool samples (a protein associated with acute gut inflammation) will be performed to assess the correlation between gut inflammation, quality of life, and response to treatment with CZP.

Has been changed to:

For axSpA patients suffering from gut inflammation, the QoL will be assessed with an inflammatory bowel disease questionnaire (IBD-Q) and, in addition to this, an analysis of calprotectin in stool and serum samples (a protein associated with acute gut inflammation) will be performed to assess the correlation between gut inflammation, quality of life, and response to treatment with CZP.

Change #7

3. STUDY OBJECTIVES

The following sentence was inserted as the last paragraph:

Subjects who meet the criteria of flare during Part B and who crossed-over to full-dose treatment (CZP 200mg Q2W) are regarded as escapers.

Change #8

Section 4.1.2.3: Secondary efficacy variables for subjects who experience a flare in Part B, paragraph 1

The following are secondary efficacy variables for subjects who experience a flare in Part B. These will be evaluated 12 weeks after escape and at Week 96, or a later timepoint, if applicable.

The minimum full-dose treatment for the escapers is 12 weeks and could extend beyond the Week 96 visit.

Has been changed to:

The following are secondary efficacy variables for subjects who experience a flare in Part B. These will be evaluated at Escape Week 12.

Bullet #3 has been modified:

- Change from Baseline in ASDAS, BASDAI, BASFI, BASMI, and sacroiliac SPARCC and ASspIMRI-a in the Berlin modification scores.

Change #9

4.1.3.1 Other efficacy variables for subjects entering Part A

Bullet #2, 3, 6, and 20 were amended

- Change from Baseline in ASDAS, BASDAI, BASFI, and BASMI
- Change from Baseline in sacroiliac SPARCC and spine ASspIMRI-a in the Berlin modification scores
- Change from Baseline in all individual ASAS core components
- Total and nocturnal spinal pain (Numeric Rating Scale [NRS])
- Correlation between fecal calprotectin, and IBD-Q

Has been changed to:

- Change from Baseline in ASDAS, BASDAI and BASMI
- Change from Baseline in sacroiliac SPARCC and ASspIMRI-a in the Berlin modification scores
- Change from Baseline in all individual ASAS core components
  - Total spinal pain (Numeric Rating Scale [NRS])
- Correlation between fecal calprotectin, serum calprotectin, IBD-Q, and CRP

Inserted bullet #2, 4, 7, 8, 9, 10, and 21

- BASDAI50 response
- ASDAS disease activity (ASDAS-ID, ASDAS-MD, ASDAS-HD, and ASDAS-vHD) and clinical improvement (ASDAS-CII, ASDAS-MI)
- Change from Baseline in nocturnal spinal pain (NRS)
- Change from Baseline in spinal mobility, as assessed by occiput to wall distance
- Change from Baseline in spinal mobility as assessed by chest expansion
- Change from Baseline in PhGADA
- Change from Baseline in serum calprotectin

Change #10

4.1.3.2 Other efficacy variables for subjects entering Part B

Bullets #6 and 18 were amended

- Change from Baseline in all individual ASAS core components
  - Total and nocturnal spinal pain (Numeric Rating Scale [NRS])
- Correlation between fecal calprotectin and IBD-Q

Has been changed to:

- Change from Baseline in all individual ASAS core components
  - Total spinal pain (NRS)
- Correlation between fecal calprotectin, serum calprotectin, IBD-Q, and CRP

Inserted bullet #1, 2, 3, 4, 5, 7, 8, 9, 10, 15, and 23

- ASAS20, ASAS40, ASAS5/6, and ASAS PR response
- BASDAI50 response
- ASDAS disease activity (ASDAS-ID, ASDAS-MD, ASDAS-HD, and ASDAS-vHD) and clinical improvement (ASDAS-CII, ASDAS-MI)
- Change from Baseline in ASDAS, BASDAI, and BASMI
- Change from randomization Baseline (Week 48) in ASDAS, BASDAI, BASFI, and BASMI
- Change from Baseline in nocturnal spinal pain (NRS)
- Change from Baseline in spinal mobility, as assessed by occiput to wall distance
- Change from Baseline in spinal mobility assessed by chest expansion
- Change from Baseline in PhGADA
- Change from randomization Baseline (Week 48) in sacroiliac SPARCC and spine ASspIMRI-a in the Berlin modification scores
- Change from Baseline in serum calprotectin

Change #11

Inserted section 4.1.3.3. Other efficacy variables for subjects who experience a flare in Part B

The following other efficacy variables for subjects who experience a flare in Part B will be evaluated at all scheduled study visits where the assessment is performed following Escape Week 0.

- ASDAS disease activity (ASDAS-ID, ASDAS-MD, ASDAS-HD, and ASDAS-vHD) and clinical improvement (ASDAS-CII, ASDAS-MI)
- ASAS20, ASAS40, ASAS5/6, and ASAS PR response
- Change from Baseline in ASDAS, BASDAI, and BASMI

- Change from randomization Baseline (Week 48) in ASDAS, BASDAI, BASFI, and BASMI
- Change from the visit at which the flare occurred in ASDAS, BASDAI, BASFI, and BASMI
- Change from Baseline in all individual ASAS core components
  - PtGADA
  - Total spinal pain (NRS)
  - BASFI
  - Average of Questions 5 and 6 of the BASDAI concerning morning stiffness
- Change from Baseline in nocturnal spinal pain (NRS)
- Change from Baseline in spinal mobility, as assessed by occiput to wall distance
- Change from Baseline in spinal mobility assessed by chest expansion
- Change from Baseline in PhGADA
- Change from Baseline in Fatigue (NRS) (from BASDAI)
- BASDAI50 response
- Change from Baseline in CRP
- Change from Baseline in ASQoL
- Change from Baseline in sacroiliac SPARCC and ASspIMRI-a in Berlin modification scores
- Change from randomization Baseline (Week 48) in sacroiliac SPARCC and ASspIMRI-a in Berlin modification scores
- Change from Escape Week 0 in sacroiliac SPARCC and ASspIMRI-a in Berlin modification scores
- Change from Baseline in WPS
- Health status as assessed by the EQ-5D: domains, VAS actual score, and change from Baseline in VAS score
- Change from Baseline in MASES
- Number of uveitis flares
- Number of IBD exacerbations
- Change from Baseline in fecal calprotectin
- Change from Baseline in serum calprotectin
- Change from Baseline in the IBD-Q
- Correlation between fecal calprotectin, serum calprotectin, IBD-Q, and CRP
- Number of psoriasis exacerbations (in subjects with concurrent psoriasis)
- Change from Baseline in all SF-36 domains, SF-36 PCS, and SF-36 MCS

- Resources utilization: concomitant medical procedures, healthcare provider consultations not foreseen by the protocol, hospitalizations/emergency room visits

Change #12

4.2.3 Pharmacogenomic variables

Blood samples will be drawn for possible genetic, genomic, and proteomic analysis at Baseline, and, for genomic and proteomics analysis only, additionally at Weeks 12, 24, 48, and 96 to enable exploratory evaluation of biomarkers relative to drug treatment and inflammatory and immune response processes. The samples will be stored at -80°C at the Central Laboratory facilities for up to 20 years or according to local laws.

Has been changed to:

Blood samples will be drawn for possible genetic, genomic, and proteomic analysis at Baseline, and, for genomic and proteomics analysis only, additionally at Weeks 12, 24, 48, 72, and 96/WD to enable exploratory evaluation of biomarkers relative to drug treatment and inflammatory and immune response processes. The samples will be stored at -80°C at the Central Laboratory facilities for up to 20 years or according to local laws.

Change #13

4.4. Safety variables

Safety variables to be assessed are AEs, physical examination, chest x-ray, and measurements of laboratory parameters (hematology, biochemistry, and urinalysis).

Adverse events will be solicited at every visit, and recorded and coded according to the latest version of the Medical Dictionary for Regulatory Activities® criteria used at UCB at the time of analysis.

Physical examination findings will be recorded in the electronic Case Report Form (eCRF) only at Screening. Clinically relevant changes in subsequent physical examinations will be recorded as AEs.

Clinical laboratory values (hematology, biochemistry, and urinalysis) will be collected and assessed at Screening, Baseline, at Weeks 12, 24, 32, 36, and every 12 weeks thereafter through to study Completion/WD Visit and at the SFU Visit 10 weeks after the last dose of study medication. C-reactive protein values will be collected and assessed at Screening, Baseline, Weeks 2, 4, 12, 24, 32, 36, 3 to 5 days prior to Week 48, 48, 50, 52, and every 4 weeks thereafter through to study Completion/WD Visit. For escapers, different schedules for clinical laboratory values and CRP apply after start of the escape treatment (refer to Table 5.2).

At Screening, Week 48, and Week 96, all subjects will have an IGRA test (QuantiFERON TB GOLD In Tube test or another WHO-validated IGRA test such as Elispot, if QuantiFERON TB GOLD In Tube test is not available locally). A chest x-ray (or, if done, computed axial tomography of the chest) at Screening (or up to 3 months prior to Screening) must be read and reported consistent with standard clinical reporting practice by an experienced 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, including the Completion/WD Visit, for signs and symptoms of latent or active TB infection and risk factors for exposure to TB using the TB questionnaire.

Has been changed to:

Safety variables to be assessed are AEs, physical examination, vital sign measurements, chest x-ray, and measurements of laboratory parameters (hematology, biochemistry, and urinalysis).

Adverse events will be solicited at every visit, and recorded and coded according to the latest version of the Medical Dictionary for Regulatory Activities® criteria used at UCB at the time of analysis.

Physical examination findings will be recorded in the electronic Case Report Form (eCRF) only at Screening. Clinically relevant changes in subsequent physical examinations will be recorded as AEs.

Clinical laboratory values (hematology, biochemistry, and urinalysis) will be collected and assessed at Screening, Baseline, at Weeks 12, 24, 32, 36, and every 12 weeks thereafter through to study Week 96/WD Visit and at the SFU Visit 10 weeks after the last dose of study medication. C-reactive protein values will be collected and assessed at Screening, Baseline, Weeks 2, 4, 12, 24, 32, 36, 3 to 5 days prior to Week 48, Week 50, Week 52, and every 4 weeks thereafter through to study Week 96/WD Visit. For escapers, different schedules for clinical laboratory values and CRP apply after start of the escape treatment (refer to Table 5.2).

At Screening, Week 48, and Week 96, all subjects will have an IGRA test (QuantiFERON TB GOLD In Tube test or another WHO-validated IGRA test such as Elispot, if QuantiFERON TB GOLD In Tube test is not available locally). A chest x-ray (or, if done, computed axial tomography of the chest) at Screening (or up to 3 months prior to Screening) must be read and reported consistent with standard clinical reporting practice by an experienced 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, including the Week 96/WD Visit, for signs and symptoms of latent or active TB infection and risk factors for exposure to TB using the TB questionnaire.

Change #14

5.1.1 Part A, paragraph 1

Period 1 (Screening Period): Up to 5 Weeks before Baseline

Eligible subjects will be informed about the study and sign the informed consent. Concomitant medications such as MTX, SSZ, hydroxychloroquine (HCQ), NSAIDs, and corticosteroids, will be verified and, if required, the washout of any medications not permitted for use during the study will be started. Concomitant medications must follow the protocol requirements in Table 6.1. Subjects will receive a physical examination. Women of childbearing age will be tested for pregnancy. Laboratory data (hematology, urine, and biochemistry tests) and a fecal

stool sample will be obtained, and treatment of latent TB (LTB), where necessary, initiated. 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. Additionally, a central reading of the x-ray will define the stratification of the subjects into the nr-axSpA or the AS subpopulation.

Has been changed to:

Period 1 (Screening Period): Up to 5 Weeks before Baseline

Eligible subjects will be informed about the study and sign the informed consent. Concomitant medications such as MTX, SSZ, hydroxychloroquine (HCQ), NSAIDs, and corticosteroids, will be verified and, if required, the washout of any medications not permitted for use during the study will be started. Concomitant medications must follow the protocol requirements in Table 6.1. Subjects will receive a physical examination and vital signs measurements will be taken. Women of childbearing age will be tested for pregnancy. Laboratory data (hematology, urine, and biochemistry tests) and treatment of latent TB (LTB), where necessary, will be collected. Subjects must undergo a TB test and complete a TB questionnaire. Patient's Global Assessment of Disease Activity, BASDAI, BASMI, spinal mobility assessments, and MRI will be performed. Additionally, a central reading of the x-ray will define the stratification of the subjects into the nr-axSpA or the AS subpopulation.

Change #15

5.1.2 Part B, period 3, last paragraph

Stool samples for fecal calprotectin will be collected for all subjects at Weeks 48 and 96/withdrawal.

Has been changed to:

Stool samples for fecal calprotectin will be collected for all subjects at Weeks 48 and 96/WD and blood samples for serum calprotectin will be collected for all subjects 3 to 5 days prior to Week 48, Week 72, and at Week 96/WD.

Change #16

5.1.3 Escape treatment, first paragraph

The interactive voice or web response system (IXRS) will be used to determine whether escape criteria are met.

Has been changed to:

The interactive voice or web response system (IXRS) will be used to determine whether flare criteria are met.

Change #17

5.1.4 Study duration per subject

For each subject, the study will last a maximum of 109 weeks, as follows:

- Up to 5 weeks of Screening Period
- 48 weeks in the Open-Label Period

- 48 weeks in the Double-Blind Period (dose reduction/withdrawal of CZP-treatment)
- A SFU Visit 10 weeks after last dose administration (Period 4)

For subjects who experience a flare during the Double-Blind Period, the study duration might be prolonged (refer to Section 6.3.2).

The end of the study is defined as the date of the last visit of the last subject in the study.

Has been changed to:

For each subject, the study will last a maximum of 109 weeks, as follows:

- Up to 5 weeks of Screening Period
- 48 weeks in the Open-Label Period
- 48 weeks in the Double-Blind Period (dose reduction/withdrawal of CZP-treatment)
- A SFU Visit 10 weeks after last dose administration (Period 4)

Of the 10 weeks interval specified for the SFU Visit, the first 2 weeks coincide with the last 2 weeks of the Double-Blind Period (ie, last 2 weeks of the 48 weeks) and the last administration is at Week 94. Hence, the maximum duration is 109 weeks.

For subjects who experience a flare during the Double-Blind Period, the study duration might be prolonged (refer to Section 6.3.2).

The end of the study is defined as the date of the last visit (SFU) of the last subject in the study.

Change #18

5.1.5 Planned number of subjects and sites

Approximately 1250 subjects will be screened in order to enroll 750 subjects into Part A, where 210 subjects are expected to meet the sustained remission criteria and be eligible for randomization into Part B. Ankylosing Spondylitis Disease Activity Score will be closely monitored during Part A of the study to project the percentage of enrolled subjects likely to achieve ASDAS-ID at the end of Part A. The enrollment will be adjusted accordingly in order to achieve the required number of 210 subjects in sustained clinical remission qualifying for Part B.

The end of the study is defined as the date of the last visit (SFU) of the last subject in the study. It is planned to enroll the subjects at approximately 95 sites.

Has been changed to:

Approximately 1250 subjects will be screened in order to enroll 750 subjects into Part A, where 210 subjects are expected to meet the sustained remission criteria and be eligible for randomization into Part B. Ankylosing Spondylitis Disease Activity Score will be closely monitored during Part A of the study to project the percentage of enrolled subjects likely to achieve sustained remission at the end of Part A. The enrollment will be adjusted accordingly in order to achieve the required number of 210 subjects in sustained clinical remission qualifying for Part B.

It is planned to enroll subjects at approximately 95 sites.

.

Change #19

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Protocol Activity	**-5 to -1**	**0**	**2**	**4**	**6 10 H**	**12**	**14 22 H**	**24**	**26 30 H**	**32**	**34 H**	**36**	**38 46 H**	**3-5 prior to W48**	**48**	**50 HN**	**52**	**54 58 HN**	**60**	**62 70 HN**	**72**	**74 82 HN**	**84**	**86 94 HN**	**96/ WD**	**SFU [a]**
Inclusion/exclusion	X	X																								
Informed consent [b]	X																									
Demographic data	X																									
Medical history (including axSpA	X																									
Vital signs [c]	X	X	X	X		X		X		X		X			X		X	X	X	X	X	X	X	X	X	X
Haematology/ urine/ biochemistry	X[d]	X[d]				X		X		X		X			X				X		X		X		X	X
CRP [e]	X	X	X	X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy testing [f]	X	X																							X	X
PE [g]	X	X				X		X				X			X				X		X		X		X	X
Extra-articular assessments	X	X		X		X		X				X			X		X		X		X		X		X	
Chest x-ray [h]	X																									
TB test [i]	X														X										X	
TB questionnaire	X	X				X		X				X			X				X		X		X		X	
Sacroiliac joint x-ray [j]	X																									
MRI [k]	X														X										X	
Stool sample [l]		X													X										X	
IBD-Questionnaire		X													X										X	
BASMI and Spinal mobility [m]	X	X	X	X		X		X				X			X		X		X		X		X		X	

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Protocol Activity	**-5 to -1**	**0**	**2**	**4**	**6 10 H**	**12**	**14 22 H**	**24**	**26 30 H**	**32**	**34 H**	**36**	**38 46 H**	**3-5 prior to W48 visit**	**48**	**50 HN**	**52**	**54 58 HN**	**60**	**62 70 HN**	**72**	**74 82 HN**	**84**	**86 94 HN**	**96/ WD**	**SFU [a]**
BASDAI [e]	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	
SF-36		X		X		X		X				X			X				X		X		X		X	
AsQoL		X	X	X		X		X				X			X				X		X		X		X	
EQ-5D		X				X		X				X			X				X		X		X		X	
MASES		X				X		X				X			X				X		X		X		X	
Total and nocturnal spinal pain		X	X	X		X		X				X			X		X		X		X		X		X	
Swollen and tender joint counts		X	X	X		X		X				X			X		X		X		X		X		X	
Patient's Global Assessment of Disease Activity [e]		X	X	X		X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	
Investigator's AS assessment		X				X		X				X			X		X		X		X		X		X	
Work Productivity Survey		X		X		X		X				X			X				X		X		X		X	
Resources utilization [n]		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
Genetics/genomics/ proteomics [o]		X				X		X							X						X				X	
Prior and Concomitant medication [p]	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
IXRS	X	X	X	X		X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X
Study drug sc on-site		X	X	X		X		X		X		X			X		X		X		X		X			
Study drug sc self-inj. at home					X		X		X		X		X													
Randomization															X											
Nurse visit at subj. home (incl. study drug sc inj.) [q]																X		X		X		X		X		
Check of sustained remission criteria [r]						X		X		X		X			X	X	X	X	X	X	X	X	X	X		
Telephone Contact [s]					X		X		X				X													

Abs=antibodies; AEs=adverse events; AS=ankylosing spondylitis; AsQoL=Ankylosing Spondylitis Quality of Life; axSpA=axial spondyloarthritis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; CZP=certolizumab pegol; EQ-5D=EuroQoL Health Status Questionnaire; H=home, no site visit; HIV=human immunodeficiency virus; HLA-B27=human leukocyte antigen B27; HN=home nurse visit at subjects home; IBD=Inflammatory bowel disease; incl.=including; inj=injection; IXRS=Interactive Voice or Web Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MRI=magnetic resonance imaging; PE=physical exam; sc=subcutaneously; SF-36=Short‑Form 36‑item Health Survey; SFU=Safety Follow-Up; SI=sacroiliac; subj=subject; TB=tuberculosis; W=Week; WD=Withdrawal; WHO=World Health Organization

[a] SFU: 10 weeks after last dose of study medication.

[b] 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 be obtained from subjects consenting also to the use of their blood samples for possible genetic, genomic, and proteomic analysis.

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

[d] Testing to rule out hepatitis B surface antigen, antibodies to hepatitis C, and antibodies at Screening only. Testing for HLA-B27 at Baseline only.

[e] To be assessed as indicated and from Week 52 onwards every 4 weeks only

[f] Pregnancy testing for women of childbearing potential will be serum testing at the Screening Visit and SFU and urine testing at Baseline and Week 96/WD Visit.

[g] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Weight is to be measured at Screening, Baseline, Week 48, and at Completion at Week 96/Withdrawal. Height will be measured at the Baseline Visit only.

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

[i] QuantiFERON TB GOLD test or another WHO-validated IGRA test such as Elispot test, if QuantiFERON TB GOLD test is not locally available. The TB tests will be repeated at Week 48 and 96 (or at Early Withdrawal Visit if medically indicated) for subjects with previously negative TB test result.

[j] Sacroiliac joint x-rays will be performed at Screening and used as the Baseline assessment for all subjects. An SIJ x-ray performed ≤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.

[k] Magnetic resonance imaging of the spine and sacroiliac joints to be performed at Screening, Week 48, and 96 or Early WD Visit if MRI was performed more than 12 weeks prior to Early WD Visit.
[l] Kit for collection of stool sample to be provided at Screening Visit. Stool sample shall be obtained prior to Baseline and provided to the Investigator at the Baseline Visit.
[m] Occiput to wall distance; chest expansion; and BASMI, which includes modified Schober test, lateral spinal flexion, cervical rotation, tragus to wall distance, and maximal intermalleolar distance.
[n] Resource utilization includes: concomitant medical procedures, health care provider consultations not foreseen by the protocol, hospitalizations/emergency room visits.
[o] Blood sample for genetic analysis at Baseline only, for genomic and proteomic analysis at all indicated timepoints.
[p] Prior medication will be at Screening only.
[q] Nurse visit at home only where approved and with agreement of subjects. Otherwise, the visit procedures will be done on-site by the site-staff.
[r] Refer to Protocol Section 3 for definition. In case of loss of sustained remission in Part B, the subject must visit the study site for the next scheduled dose of study medication. The Investigator will initiate the escape treatment as appropriate. Refer to Table 5.2 for details.
[s] Subjects will be contacted by telephone about every 4 weeks in between the on-site visits.

Has been changed to

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A															PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**														**3 (Double-Blind)**											**4**
Week (W)	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU[b]**
Protocol Activity																											
Inclusion/exclusion	X	X																									
Informed consent [c]	X																										
Demographic data	X																										
Medical history (including axSpA and extra-articular manifestations history)	X																										
Vital signs [d]	X	X	X	X		X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology/urine/ biochemistry	X[e]	X				X		X		X		X		X					X		X		X		X	X	X
CRP [f]	X	X	X	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	
Pregnancy testing [g]	X	X																								X	X
PE [h]	X	X				X		X				X			X				X		X		X		X	X	X
Extra-articular assessments	X	X		X		X		X				X			X		X		X		X		X		X	X	

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Week (W) **Protocol Activity**	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU[b]**
Chest x-ray [i]	X																									
TB test [j]	X														X										X	
TB questionnaire	X	X				X		X				X			X				X		X		X		X	
Sacroiliac joint x-ray [k]	X																									
MRI [l]	X														X										X	
Stool sample [m]		X													X										X	
Serum calprotectin		X				X		X						X							X				X	
IBD-Questionnaire		X												X											X	
BASMI and Spinal mobility [n]	X	X	X	X		X		X				X			X		X		X		X		X		X	
BASDAI [f]	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	
SF-36		X		X		X		X				X		X					X		X		X		X	
AsQoL		X	X	X		X		X				X		X					X		X		X		X	
EQ-5D		X				X		X				X		X					X		X		X		X	

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Week (W)	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU[b]**
Protocol Activity																										
MASES		X				X		X				X			X				X		X		X		X	
Total and nocturnal spinal pain		X	X	X		X		X				X		X			X		X		X		X		X	
Swollen and tender joint counts		X	X	X		X		X				X			X		X		X		X		X		X	
Patient's Global Assessment of Disease Activity [f]	X	X	X	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	
Physician's Global Assessment of Disease Activity		X				X		X				X			X		X		X		X		X		X	
Work Productivity Survey		X		X		X		X				X			X				X		X		X		X	
Resources utilization [o]		X				X		X				X			X				X		X		X		X	
CZP plasma concentration/ ADAb		X		X		X		X						X					X		X		X		X	X
Biomarker		X		X		X		X						X					X		X		X		X	X
Genetics		X												X												

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Week (W) **Protocol Activity**	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU [b]**
Genomics/ proteomics		X				X		X						X							X				X	
Prior and Concomitant medication[p]	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
IXRS	X	X	X	X		X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X
Study drug sc onsite		X	X	X		X		X		X		X			X		X		X		X		X			
Study drug sc self-inj. at home					X		X		X		X		X													
Randomization															X											
Nurse visit at subj. home (incl. study drug sc inj.) [q]																X		X		X		X		X		
Check of sustained remission criteria [r]						X		X		X		X			X	X	X	X	X	X	X	X	X	X		
Telephone Contact [s]					X		X		X				X													

Abs=antibodies; ADAb= anti-CZP antibody concentration; AEs=adverse events; AS=ankylosing spondylitis; AsQoL=Ankylosing Spondylitis Quality of Life; axSpA=axial spondyloarthritis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; CZP=certolizumab pegol; EQ-5D=EuroQoL Health Status Questionnaire; H=home, no site visit; HIV=human immunodeficiency virus; HLA-B27=human leukocyte antigen B27; HN=home nurse visit at subject's home; IBD=Inflammatory bowel disease; incl.=including; inj=injection; IXRS=Interactive Voice or Web Response System; MASES=Maastricht Ankylosis Spondylitis

Enthesitis Score; MRI=magnetic resonance imaging; PE=physical exam; sc=subcutaneously; SF-36=Short‑Form 36‑item Health Survey; SFU=Safety Follow-Up; SI=sacroiliac; subj=subject; TB=tuberculosis; W=Week; WD=Withdrawal; WHO=World Health Organization

[a] Assessments conducted 3 to 5 days prior to Week 48 will serve as the qualification assessments for subjects determined to be eligible for randomization into Part B at Week 48.

[b] SFU: 10 weeks after last dose of study medication.

[c] 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 be obtained from subjects consenting also to the use of their blood samples for possible genetic, genomic, and proteomic analysis.

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

[e] Testing to rule out hepatitis B surface antigen, antibodies to hepatitis C, antibodies to HIV and HLA-B27 at Screening only.

[f] To be assessed as indicated and from Week 52 onwards every 4 weeks only.

[g] Pregnancy testing for women of childbearing potential will be serum testing at the Screening Visit and SFU and urine testing at Baseline and Week 96/WD Visit.

[h] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Weight is to be measured at Screening, Baseline, Week 48, and at Week 96/WD. Height will be measured at the Baseline Visit only.

[i] Screening chest x-ray must have occurred within 3 months prior to Screening Visit and should be repeated only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure).

[j] QuantiFERON TB GOLD test or another WHO-validated IGRA test such as Elispot test, if QuantiFERON TB GOLD test is not locally available. The TB test will be repeated at Week 48 and 96 (or at WD Visit if medically indicated) for subjects with previously negative TB test result.

[k] Sacroiliac joint x-rays will be performed at Screening and used as the Baseline assessment for all subjects. An SIJ x-ray performed ≤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.

[l] Magnetic resonance imaging of the spine and sacroiliac joints to be performed at Screening, Week 48, and 96 or WD Visit if MRI was performed more than 12 weeks prior to WD Visit.

[m] Kit for collection of stool sample to be provided at Screening Visit. Stool sample shall be obtained prior to Baseline and provided to the Investigator at the Baseline Visit.

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

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

[p] Prior medication will be at Screening only.

[q] Nurse visit at home only where approved and with agreement of subjects. Otherwise, the visit procedures will be done onsite by the site staff.

[r] Refer to Protocol Section 3 for definition. In case of loss of sustained remission in Part B, the subject must visit the study site for the next scheduled dose of study medication. The Investigator will initiate the escape treatment as appropriate. Refer to Table 5.2 for details.

[s] Subjects will be contacted by telephone about every 4 weeks in between the onsite visits.

Change #20

Table 5.2: Schedule of study assessments for all subjects experiencing a flare in Part B

	Part B for subjects experiencing a flare					
Study-Period	3B					
Visit / week (W) on escape treatment	**0**	**2**	**4**	**6 to 10 H/H N [a]**	**12 (and every 12 weeks thereafter) [b]**	**every 2 weeks in between [c] H/HN [a]**
Protocol Activity						
Vital signs [d]	X	X	X		X	
Haematology/ urine/ biochemistry	X				X	
CRP [e]	X	X	X	X [f]	X	X [f]
Stool sample [g]	X				X	
IBD-Questionnaire [g]	X				X	
PE	X	X	X		X	
Extra-articular assessments	X		X		X	
MRI [h]	X				X	
TB questionnaire	X				X	
BASMI & Spinal mobility [i]	X	X	X		X	
BASDAI	X	X	X	X [f]	X	X [f]
BASFI	X	X	X		X	
SF-36	X		X		X	
AsQoL	X	X	X		X	
EQ-5D	X		X		X	
MASES	X	X	X		X	
Total and nocturnal spinal pain	X	X	X		X	
Patient's Global Assessment of Disease Activity	X	X	X	X [f]	X	X [f]
Investigator's AS assessment	X	X	X		X	

Table 5.2: Schedule of study assessments for all subjects experiencing a flare in Part B

Study-Period	**3B**					
Visit / week (W) on escape treatment / **Protocol Activity**	**0**	**2**	**4**	**6 to 10 H/HN [a]**	**12 (and every 12 weeks thereafter) [b]**	**every 2 weeks in between [c] H/HN [a]**
Work Productivity Survey	X		X		X	
Resources utilization [j]	X		X		X	
CZP plasma concentration/anti-CZP Abs / Biomarker	X	X	X		X	
Concomitant medication	X	X	X		X	
AEs	X	X	X		X	
IXRS	X	X	X	X	X	X
Study drug sc on-site	X	X	X		X	
Study drug sc self-inj. at home				X		X
Telephone Contact [k]				X		X

Has been changed to:

Table 5.2: Schedule of study assessments for all subjects experiencing a flare in Part B

	Part B for subjects experiencing a flare					
Study-Period	**3B**					
Visit / week (W) on escape treatment / **Protocol Activity**	**0**	**2**	**4**	**6 to 10 H/HN [a]**	**12 (and every 12 weeks thereafter) [b]**	**every 2 weeks in between [c] H/HN [a]**
Vital signs [d]	X	X	X		X	
Hematology/urine/ biochemistry	X				X	
CRP [e]	X	X	X	X [f]	X	X [f]
Stool sample [g]	X				X	
Serum calprotectin [g]	X				X	
IBD-Questionnaire [g]	X				X	

Table 5.2: Schedule of study assessments for all subjects experiencing a flare in Part B

	Part B for subjects experiencing a flare					
Study-Period	**3B**					
Visit / week (W) on escape treatment	**0**	**2**	**4**	**6 to 10 H/HN [a]**	**12 (and every 12 weeks thereafter) [b]**	**every 2 weeks in between [c] H/HN [a]**
Protocol Activity						
PE	X	X	X		X	
Extra-articular assessments	X		X		X	
MRI [h]	X				X	
TB questionnaire	X				X	
BASMI & Spinal mobility [i]	X	X	X		X	
BASDAI	X	X	X	X [f]	X	X [f]
BASFI	X	X	X		X	
SF-36	X		X		X	
AsQoL	X	X	X		X	
EQ-5D	X		X		X	
MASES	X	X	X		X	
Total and nocturnal spinal pain	X	X	X		X	
Patient's Global Assessment of Disease Activity	X	X	X	X [f]	X	X [f]
Physician's Global Assessment of Disease Activity	X	X	X		X	
Work Productivity Survey	X		X		X	
Resources utilization [j]	X		X		X	
CZP plasma concentration/ADAb	X	X	X		X	
Biomarker	X	X	X		X	
Concomitant medication	X	X	X		X	

Table 5.2: Schedule of study assessments for all subjects experiencing a flare in Part B

	Part B for subjects experiencing a flare					
Study-Period	3B					
Visit / week (W) on escape treatment / **Protocol Activity**	**0**	**2**	**4**	**6 to 10 H/HN [a]**	**12 (and every 12 weeks thereafter) [b]**	**every 2 weeks in between [c] H/HN [a]**
AEs	X	X	X		X	
IXRS	X	X	X	X	X	X
Study drug sc onsite	X	X	X		X	
Study drug sc self-inj. at home				X		X
Telephone Contact [k]				X		X

Change #21

Section 6.1 Inclusion criteria

Criterion #6 (sub-bullet #3)

- Spinal pain >4 on a 0 to 10 NRS (from BASDAI Item 2)

Has been changed to:

- Spinal pain ≥4 on a 0 to 10 NRS (from BASDAI Item 2)

Change #22

6.2 Exclusion criteria

Criterion #8

Table 6.1 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 postscreening visit. Stable dose of analgesics (including narcotics) are permitted throughout the study.

NSAIDs (including cyclooxygenase 2 [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 postscreening visit. NSAID dose should be stable until Week 96 (if subjects have to decrease or stop taking medication due to safety reasons, they may reduce their dose and continue in the study).
SAARDs[b]: SSZ and/or HCQ and/or MTX and/or LFN and /or AZA	Maximum allowed: SSZ ≤3g daily HCQ ≤400mg daily MTX ≤25mg weekly AZA ≤150mg/day LFN ≤20mg/day (see exclusion criteria for washout requirements)	SAARD use initiated and or any change in the dose regimen in the 28 days prior to the Baseline Visit. No change is permitted in the route of administration for MTX (im, sc, or oral) 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	SAARDs should be stable until Week 96 (if a subject has to decrease or stop taking medications due to safety reasons, they may reduce their SAARDs and continue in the study).

Has been changed to:

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 postscreening visit. Stable dose of analgesics (including narcotics) are permitted throughout the study.

Drug class	Dose	Exclusion criteria	Study Visits
NSAIDs (including cyclooxygenase 2 [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 postscreening visit. NSAID dose can be down-titrated at Investigator discretion, if clinically indicated, until Week 28, after which NSAID treatment should remain as stable as possible. NSAID dose should be stable until Week 96 (if subjects have to decrease or stop taking medication due to safety reasons, they may reduce their dose and continue in the study).
SAARDs[b]: SSZ and/or HCQ and/or MTX and/or LFN and /or AZA	Maximum allowed: SSZ ≤3g daily HCQ ≤400mg daily MTX ≤25mg weekly AZA ≤150mg/day LFN ≤20mg/day	SAARD use initiated and/or any change in the dose regimen in the 28 days prior to the Baseline Visit. No change is permitted in the route of administration for MTX (im, sc, or oral) in the 28 days prior to the Baseline Visit	SAARDs should be stable until Week 96 (if a subject has to decrease or stop taking medications due to safety reasons, they may reduce their SAARDs and continue in the study).

Change #23

6.2 Exclusion Criteria

13 Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the study or within 3 months following the last dose of the investigational product.

Has been changed to:

13 Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the study or within 10 weeks (or – for participating countries of the EU – 5 months in accordance with the SmPC) following the last dose of the investigational product.

Change #24

6.3.2 Escape criteria, paragraphs 2, 3, and 4

Subjects escaping from placebo to full-dose CZP (200mg Q2W) will receive a loading dose of CZP (400mg Q2W) at the 3 consecutive visits after the flare. Subjects escaping from half-dose CZP to full-dose CZP will receive CZP 200mg Q2W at the 3 consecutive visits after the flare. In

order to maintain the blind, subjects escaping from half-dose CZP to full-dose CZP will receive a placebo administration and a CZP 200mg administration at these 3 visits.

Subjects randomized to the CZP full-dose (200mg Q2W) treatment during the Double-Blind Period who qualify for escape will remain on their current treatment allocation. As with subjects escaping from half-dose CZP to full-dose CZP, these subjects will receive a placebo and CZP 200mg injection at the 3 visits after the flare in order to maintain the blind to the randomized treatment.

After the loading dose, all escaped subjects will continue full-dose CZP treatment in an open-label fashion.

Has been changed to:

6.3.2 Escape treatment

Subjects escaping from placebo to full-dose CZP (200mg Q2W) will receive a loading dose of CZP (400mg Q2W; 2 injections) at the 3 consecutive visits after the flare. Subjects escaping from half-dose CZP to full-dose CZP will receive a loading dose of CZP 200mg Q2W at the 3 consecutive visits after the flare. In order to maintain the blind, subjects escaping from half-dose CZP to full-dose CZP will receive a placebo administration and a CZP 200mg administration (a total of 2 injections) at these 3 visits (Figure 7.1).

Subjects randomized to the CZP full-dose (200mg Q2W) treatment during the Double-Blind Period who qualify for escape will remain on their current treatment allocation. As with subjects escaping from half-dose CZP to full-dose CZP, these subjects will receive a placebo and CZP 200mg injection (a total of 2 injections) at the 3 visits after the flare in order to maintain the blind to the randomized treatment.

After the loading dose (200mg Q2W or 400mg Q2W), all escaped subjects will continue full-dose CZP treatment in an open-label fashion.

Change #25

7.2.1 Treatment administration, paragraphs 2 and 3

Study medication will be given sc by dedicated and adequately trained site personnel. Suitable areas for administrations are the lateral abdominal wall and upper outer thigh. During each dosing visit, if 2 injections are being administered (ie, CZP 400mg as 2 injections of 200mg each) each of the 2 injections should be administered at a separate injection site.

Has been changed to:

Study medication will be given sc by dedicated and adequately trained site personnel or the subject may start self-administering from Week 6 after training at Week 2 and Week 4.

Suitable areas for administrations are the lateral abdominal wall and upper outer thigh. During each dosing visit, if 2 injections are being administered (ie, loading dose CZP 400mg as 2 injections of 200mg each) each of the 2 injections should be administered at a separate injection site.

Change #26

7.3 Packaging

Part A

Each site will receive during Period 2 (Open-Label Period: Week 0 [Baseline] to Week 47) uniquely numbered PFSs of CZP, which will be packaged in individual labeled protective containers (clamshells).

Part B

Each site will receive during Period 3 (Double-Blind Period: Week 48 to Week 96, placebo controlled) uniquely numbered PFSs of CZP or placebo, which will be packaged in individual labeled protective containers (clamshells).

Has been changed to:

For Part A and B, CZP and placebo are packaged and labeled according to Good Manufacturing Practice 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.

Change #27

7.8.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications/treatments are permitted during the study, from Baseline onward, with restrictions as specified:

- NSAIDs/cyclooxygenase 2 (COX-2) inhibitors: doses should be stable throughout the study and ad hoc as needed (prn) inhibitors should not be used 24 hours prior to any post-Screening study visit. No change in dose or dose regimen is allowed during the study except for reasons of safety, where the NSAIDs/COX-2 inhibitors dose may be decreased or discontinued.

Has been changed to:

- NSAIDs/cyclooxygenase 2 (COX-2) inhibitors: doses should be stable throughout the study and ad hoc as needed (prn) inhibitors should not be used 24 hours prior to any post-Screening study visit. No change in dose or dose regimen is allowed during the study except for reasons of safety, where the NSAIDs/COX-2 inhibitors dose may be decreased or discontinued. NSAID dose may be down-titrated at Investigator discretion. The reduction in NSAID dose if clinically indicated is permitted at the discretion of the Investigator until Week 28, however after that timepoint the NSAID treatment should remain stable as much as possible.

Change #28

7.8.3 Rescue Medication

Escape medication is as described in Section 5.1.3.

Has been changed to:

Escape treatment is as described in Section 5.1.3.

Change #29

7.10 Randomization and numbering of subjects

To enroll a subject (Week 0 [Baseline]), the Investigator or designee will contact the IXRS and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the Investigator or designee and the IXRS regarding a particular subject. Subject numbers and kit numbers will be tracked via the IXRS.

Randomization will be stratified on:

- Geographic region
- mNY classification

Has been changed to:

To enroll a subject (Screening), the Investigator or designee will contact the IXRS and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the Investigator or designee and the IXRS regarding a particular subject. Subject numbers and kit numbers will be tracked via the IXRS.

Randomization will be stratified on:

- Geographic region (North America, Western Europe, Eastern Europe, and Asia)
- mNY classification

Change #30

8.1 Screening Visit has been changed to Screening Visit (up to 5 weeks)

Modified bullets #4, 7, and 8

- Washout of excluded medications
- Hematology, biochemistry, and urine for clinical laboratory values (includes a serum pregnancy test for women of childbearing potential, and testing to rule out hepatitis B surface antigen, antibodies to hepatitis C, antibodies to HIV, and CRP)
- Physical examination (including weight, height, evaluation of signs and symptoms of active TB and risk factors for exposure to TB) and extra-articular assessment

Has been changed to:

- Washout of prohibited medications
- Hematology, biochemistry, and urine for clinical laboratory values (includes a serum pregnancy test for women of childbearing potential, HLA-B27 and testing to rule out hepatitis B surface antigen, antibodies to hepatitis C, antibodies to HIV, and CRP)
- Physical examination (including weight, evaluation of signs and symptoms of active TB and risk factors for exposure to TB) and extra-articular assessment

Inserted bullet #16 and 18

- PtGADA
- Fecal sample kit provided to the subject

Deleted bullet #17

- AEs

Change #31

8.2 Baseline Visit (Week 0)

- Blood samples will be collected for hematology, biochemistry analyses (including HLA-B27), CRP
- Investigator's AS assessments (PhGADA)
- Plasma sample for CZP concentration, anti-CZP antibodies; and biomarkers

Has been changed to:

- Blood samples will be collected for hematology, biochemistry analyses, serum calprotectin, and CRP
- PhGADA
- Plasma sample for CZP concentration, ADAb
- Plasma sample for biomarkers, if applicable

Modified bullet #24:

- Stool sample provided by the subject for fecal calprotectin evaluation

Change #32

8.3 Weeks 2 to 96/WD onsite visits section title has been modified and has been divided into subsections:

8.3.1 Weeks 2, 4, 12, 24, 32, 36, 48, 52, 60, 72, 84, and 96/WD (± 3 Days)

Assessments at these onsite visits include:

- Vital signs: pulse rate, systolic and diastolic blood pressures, temperature will be measured (all visits). If a subject experiences an AE, respiration rate will be measured in addition.
- Blood samples will be collected for hematology and biochemistry analyses (at Weeks 12, 24, 32, 36, 60, 72, 84, and at Week 96/WD), and CRP (at Weeks 2, 4, 12, 24, 32, 36, and from Week 52 onwards every 4 weeks only).
- Urine pregnancy testing for women of childbearing potential will be at Week 96/WD only.
- Urine will be collected for urinalysis (at Weeks 12, 24, 32, 36, 48, 60, 72, 84, and at Week 96/WD).
- Physical examination (at Weeks 12, 24, 36, 48, 60, 72, 84, and at Week 96/WD), including weight at Week 48 and at Week 96/WD.

- Extra-articular assessments (at Weeks 4, 12, 24, 36, 48, 52, 60, 72, 84, and at Week 96/WD).
- TB test (at Week 48 and at Week 96/WD only).
- TB questionnaire (at Weeks 12, 24, 36, 48, 60, 72, 84, and at Week 96/WD).
- MRI (at Week 48 and at Week 96/WD only).
- BASMI and spinal mobility (at Weeks 2, 4, 12, 24, 36, 48, 52, 60, 72, 84, and at Week 96/WD only).
- BASDAI (at Weeks 2, 4, 12, 24, 32, 36, 52, 60, 72, 84, and at Week 96/WD).
- BASFI (at Weeks 2, 4, 12, 24, 36, 60, 72, 84, and at Week 96/WD only).
- SF-36 (at Weeks 4, 12, 24, 36, 60, 72, 84, and at Week 96/WD only).
- ASQoL (at Weeks 2, 4, 12, 24, 36, 60, 72, 84, and at Week 96/WD only).
- EQ-5D (at Weeks 12, 24, 36, 60, 72, 84, and at Week 96/WD only).
- IBD-Q (at Week 96/WD only).
- MASES (at Weeks 12, 24, 36, 48, 60, 72, 84, and at Week 96/WD only).
- Total spinal pain NRS and nocturnal spinal pain NRS (at Weeks 2, 4, 12, 24, 36, 52, 60, 72, 84, and at Week 96/WD only).
- Swollen and tender joint counts (at Weeks 2, 4, 12, 24, 36, 48, 52, 60, 72, 84, and at Completion at Week 96/WD only).
- PtGADA (at Weeks 2, 4, 12, 24, 32, 36, and from Week 52 onwards every 4 weeks only).
- PhGADA (at Weeks 12, 24, 36, 48, 52, 60, 72, 84, and at Week 96/WD only).
- WPS (at Weeks 4, 12, 24, 36, 48, 60, 72, 84, and at Week 96/WD only).
- Resource utilization (at Weeks 12, 24, 36, 48, 60, 72, 84, and at Week 96/WD only).
- Plasma for CZP concentration and ADAb (at Weeks 4, 12, 24, 60, 72, 84, and at Week 96/WD only).
- Plasma for biomarkers (at Weeks 4, 12, 24, 60, 72, 84, and at Week 96/WD only), if applicable.
- Genomics and proteomics (at Weeks 12, 24, 72, and at Week 96/WD only), if applicable.
- Stool sample will be collected for fecal calprotectin at Week 48 and at Week 96/WD only.
- Blood sample will be collected for serum calprotectin at Week 12, Week 24, Week 72 and Week 96/WD only.
- Concomitant medication
- AEs
- Contact IXRS to obtain next kit numbers

- Study drug administration (after all other visit assessments are completed and laboratory samples are drawn) (all visits at Week 96/WD).
- Randomization at Week 48.
- Check of sustained remission criteria (all visits except Weeks 2, 4, and Week 96/WD visit).

8.3.2 3 to 5 days prior to Week 48.

- Blood samples will be collected for hematology and biochemistry analyses and CRP
- BASDAI
- BASFI
- SF-36
- ASQoL
- EQ-5D
- IBD-Q
- Total spinal pain NRS and nocturnal spinal pain NRS
- PtGADA
- Plasma for CZP concentration and ADAb
- Plasma for biomarkers
- Genetics
- Blood sample will be collected for serum calprotectin
- AEs

Change #33

18.4 Weeks 6 to 94 home visits and home nurse visits section title has been modified and has been divided into subsections:

8.4.1 Home visits during Part A

Assessments at these home visits include:

- Study drug self-administration at home (at Weeks 6, 8, 10, 14, 16, 18, 20, 22, 26, 28, 30, 34, 38, 40, 42, 44, and 46)
- Subjects will be contacted by telephone in between the onsite visits (at Weeks 6 to 10, 14 to 22, 26 to 30, and 38 to 46)

8.4.2 Home and home nurse visits during Part B

Assessments at these home and nurse visits include:

- Vital signs: pulse rate, systolic and diastolic blood pressures, temperature will be measured. If a subject experiences an AE, respiration rate will be measured in addition (at Week 50, Weeks 54 to 58, 62 to 70, 74 to 82, and 86 to 94 only)

- CRP and PtGADA (at Weeks 50, 56, 64, 68, 76, 80, 88, and 92)
- BASDAI (at Weeks 50, 56, 64, 68, 76, 80, 88, and 92)
- Contact IXRS to report kit number (all Visit at Weeks 50, 54 to 58, 62 to 70, 74 to 82, and 86 to 94)
- Nurse visit at subject home including to perform study medication administration (at Weeks 50, 54, 56, 58, 62, 64, 66, 68, 70, 74, 76, 78, 80, 82, 86, 88, 90, 92, and 94)
- Check of sustained remission criteria (at Weeks 50, 56, 64, 68, 76, 80, 88, and 92)

Change #34

8.5 Study procedures after flare until the final assessment visit at Week 96/WD

- Stool sample will be collected for fecal calprotectin at Escape Weeks 0 and 12
- Patient's Global Assessment of Disease Activity at Escape Weeks 0, 2, 4, and every 4 weeks thereafter until the final assessment visit at Week 96/WD
- Investigator's AS Assessment at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- Plasma for CZP concentration, anti CZP antibodies, and biomarkers at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD

Has been changed to:

- Stool sample will be collected for fecal calprotectin and blood sample for serum calprotectin at Escape Weeks 0 and 12
- PtGADA at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- PhGADA at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- Plasma for CZP concentration and ADAb at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD
- Plasma for biomarkers at Escape Weeks 0, 2, 4, 12, and every 12 weeks thereafter until the final assessment visit at Week 96/WD, if applicable

Change #35

8.6 Safety Follow Up Visit

- Plasma for CZP concentration, anti-CZP antibodies, and biomarkers

Has been changed to:

- Plasma for CZP concentration and ADAb
- Plasma for biomarkers

Change #36

9.1.1. ASAS20, ASAS40, 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:

- Patient's Global Assessment of Disease Activity (see Section 9.2.3)
- Pain assessment (the average of total spinal pain NRS score)

Has been changed to:

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:

- Patient's Global Assessment of Disease Activity (see Section 9.2.3)
- Pain assessment (the total spinal pain NRS score)

The following sentence has been added to this section:

The ASAS assessments per visit are described in the schedule of study assessments Table 5.1.

Change #37

9.1.7. Ankylosing spondylitis disease activity score (ASDAS)

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).

Has been changed to:

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

Change #38

9.2.4 SF-36

The MCIDs for SI-36 domains and component summaries are 5 and 2.5 points respectively (Strand et al, 2005).

Has been changed to:

The MCIDs for SI-36 domains and component summaries are 2 to 4 points and 2 to 3 points respectively (Ware et al, 2007).

Change #39

9.2.7. Physician's global assessment of disease activity

This assessment by the Investigator should be made without any knowledge of the PhGADA.

Has been changed to:

This assessment by the Investigator should be made without any knowledge of the PtGADA.

Change #40

9.2.9 Health status (EQ-5D)

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

Has been changed to:

The EQ-5D is comprised of a 5-item health status measures and a visual analog rating scale. 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 scored levels for 5 dimensions can be combined in a 5-digit number describing the respondent's health profile or can be converted into a single summary index. The published mean Minimally Important Difference (MID) for the index value is 0.074 (range -0.011 to 0.140) and the SRM of 0.24 (range -0.05 to 0.43) (Walters et al, 2005). The EQ-5D VAS records the respondent's self-rated health status on a vertical 20cm scale, 0 to 100 graduated (0=worst imaginable health status, 100=best imaginable health status). The MID for VAS of 7 in cancer patients was published in 2007 by Pickard et al. (Pickard et al, 2007).

Change #41

9.2.12 Fecal calprotectin

The calgranulins, S100A8/S100A9 and S100A12, are calcium-binding proteins of the S100 family. They are released from activated monocytes and granulocytes at local sites of inflammation during the early phase of the immune response. Extracellularly, they exert important pro-inflammatory effects, thereby providing stimulation and amplification of the innate immune reaction. Calgranulins can be measured in serum and stool, and have been found to be very sensitive markers of innate immune activation. Moreover, the S100A8/S100A9 heterodimer, also called calprotectin, has been established for a long time as a fecal marker of disease activity in inflammatory bowel disease (Foell et al, 2009; Foell et al, 2007).

For all subjects, fecal calprotectin will be examined for gut inflammation as described in the schedule of study assessments Table 5.1. Fecal calprotectin will be measured at Baseline, Week 48 and Week 96 for the completers. For escapers, an additional sample will be collected at the time when they are escaping (Week 0) and 12 weeks thereafter.

Has been changed to:

9.2.12 Fecal and serum calprotectin

The calgranulins, S100A8/S100A9 and S100A12, are calcium-binding proteins of the S100 family. They are released from activated monocytes and granulocytes at local sites of inflammation during the early phase of the immune response. Extracellularly, they exert important pro-inflammatory effects, thereby providing stimulation and amplification of the innate immune reaction. Calgranulins can be measured in serum and stool, and have been found to be very sensitive markers of innate immune activation. Moreover, the S100A8/S100A9

heterodimer, also called calprotectin, has been established for a long time as a fecal marker of disease activity in inflammatory bowel disease (Foell et al, 2009; Foell et al, 2007).

For all subjects, fecal and serum calprotectin will be examined for gut inflammation as described in the schedule of study assessments Table 5.1. Fecal calprotectin will be measured at Baseline, Week 48 and Week 96 and serum calprotectin will be measured at Baseline, Week 12, Week 24, 3 to 5 days prior to Week 48, Week 72, and Week 96for the completers. For escapers, an additional sample will be collected at the time when they are escaping (Week 0) and 12 weeks thereafter.

Change #42

9.2.13 Inflamatory Bowel Disease Questionnaire assessment

The IBD-Q remission is defined as an IBD-Q total score ≥170 points (Irvine et al, 1994).

Has been changed to:

The IBD-Q remission is defined as an IBD-Q total score ≥170 points (Guyatt et al. 1989).

Change #43

10 Assessment of Pharmacokinetics and Pharmacogenomics Variable(s)

Blood samples will be drawn for possible genetic, genomic, and proteomic analysis at Baseline (Week 0), and for genomic and proteomics analysis only, at Weeks 12, 24, 48, 72, and at Completion at Week 96/WD to enable exploratory evaluation of biomarkers relative to drug treatment and inflammatory and immune response processes.

Has been changed to:

Blood samples will be drawn for possible genetic, genomic, and proteomic analysis at Baseline (Week 0), and for genomic and proteomics analysis only, at Weeks 12, 24, 3 to 5 days prior to Week 48, 72, and at Completion at Week 96/WD to enable exploratory evaluation of biomarkers relative to drug treatment and inflammatory and immune response processes.

Change #44

12.6 Laboratory Measurements

Hematology, biochemistry, and urinalysis samples will be taken at Screening, Baseline (Week 0), Weeks 12, 24, 32, 36, 48, 60, 72, 84, 96/WD, and at the SFU Visit (10 weeks after the last dose). Testing for hepatitis B surface antigen and antibodies to hepatitis C and HIV will be performed at Screening. Screening for HLA-B27 will be performed at Baseline only.

Has been changed to:

Hematology, biochemistry, and urinalysis samples will be taken at Screening, Baseline (Week 0), Weeks 12, 24, 32, 36, 3 to 5 days prior to 48, 60, 72, 84, 96/WD, and at the SFU Visit (10 weeks after the last dose). Testing for HLA-B27, hepatitis B surface antigen, and antibodies to hepatitis C and HIV will be performed at Screening.

Change #45

13.2.1 Definition of source data

The following sentences have been added to this section:

The following data will be recorded directly in the ePRO tablet and will not appear in a source document as defined above:

- Patient Reported Outcome questionnaires: SF-36, EQ-5D, PtGADA, BASDAI, BASFI, ASQoL, IBD-Questionnaire, Work Productivity Survey, Total and Nocturnal Spinal Pain Questionnaire

Change #46

13.3.1 Case report form completion

This study will also use an electronic device (Site Tablet) to capture the PhGADA and joint counts (see Section 13.3.2).

Has been changed to:

This study will also use an electronic device (Site Tablet) to capture patient reported outcomes (see Section 13.3.2).

Change #47

13.3.2 Electronic reporting outcome

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. Physicians' data (joint counts and PhGADA) will be entered in the eCRF or collected on worksheets.

Change #48

14.1 Definition of analysis sets

Inserted bullet #4, 5, 9, and 10

- The Flared Set (FS) will consist of all subjects from the RS who experience a flare in Part B.
- The Part B Full-Dose Set (FDS) will include all subjects from the RS who ever received a dose of CZP Q2W during Part B (including escape treatment).
- The Pharmacokinetic Set A (PKSA) will consist of all subjects from the OLS who provide at least 1 PK sample during Part A.
- The Pharmacokinetic Set B (PKSB) will consist of all subjects from the SS who provide at least 1 PK sample during Part B.

Change #49

14.2 General statistical considerations

All efficacy analyses for Part B will be performed using the RS. The FAS and PPS will be used for a sensitivity analysis on the primary endpoint only. Efficacy summaries for variables collected in Part A will be based on the OLS.

The statistical analysis of the primary efficacy variable will account for the testing of multiple doses by using a fixed sequence testing procedure. The proportion of subjects who do not experience a flare (where flare is defined as ASDAS ≥2.1 on 2 consecutive visits or ASDAS >3.5 at any visit) will be compared between each CZP dose and placebo. The predefined order of hypotheses testing, each at a 2-sided 0.05 significance level for the comparison between the given CZP dose and placebo, will be performed in the sequence shown below:

1. CZP 200mg Q2W vs placebo
2. CZP 200mg Q4W vs placebo

The second test is performed only if the first test is significant at the 0.05 level.

A secondary objective of key importance in this study is to compare the efficacy of the full-dose to the half-dose. In order to evaluate this objective, a 2-sided 95% confidence interval (CI) for the difference in the proportion of subjects who do not experience a flare (CZP 200mg Q2W minus CZP 200mg Q4W) will be constructed. If the lower limit of the interval does not extend beyond the negative of the noninferiority margin of 15%, then noninferiority of the CZP 200mg Q4W dose to the CZP 200mg Q2W dose will have been established. This noninferiority test will be conducted only if both CZP doses are found to be statistically superior to placebo, as described above.

Has been changed to:

All efficacy analyses for Part B will be performed using the RS. The FAS and PPS will be used for a sensitivity analysis on the primary endpoint only. Efficacy summaries for variables collected in Part A will be based on the OLS.

Summaries at the Week 48 timepoint for laboratory data and data collected via electronic device (Site Tablet) will be based on the assessments conducted 3 to 5 days prior to the Week 48 clinic visit.

The statistical analysis of the primary efficacy variable will account for the testing of multiple doses by using a fixed sequence testing procedure. The proportion of subjects who do not experience a flare (where flare is defined as ASDAS ≥2.1 on 2 consecutive visits or ASDAS >3.5 at any visit) will be compared between each CZP dose and placebo. The predefined order of hypotheses testing, each at a 2-sided 0.05 significance level for the comparison between the given CZP dose and placebo, will be performed in the sequence shown below:

1. CZP 200mg Q2W vs placebo
2. CZP 200mg Q4W vs placebo

The second test is performed only if the first test is significant at the 0.05 level.

Change #50

14.3.2.1 Part A analysis

The percentage of subjects achieving sustained remission, ASDAS-MI, and ASDAS-CII at Week 48 will be summarized by treatment group using descriptive statistics (counts and percentages). Separate summaries will be done using NRI and observed case data.

Ankylosing Spondylitis Disease Activity Score disease activity at Week 48 will also be summarized by treatment group using descriptive statistics, where counts and percentages are reported for each of the 4 categories. Two summaries will be provided: 1 will derive disease activity at Week 48 using last observation carried forward (LOCF, impute using the last post-Baseline nonmissing result) for missing values and the other will be based on observed case data.

Has been changed to:

The percentage of subjects achieving sustained remission, ASDAS-MI, and ASDAS-CII at Week 48 will be summarized using descriptive statistics (counts and percentages). Separate summaries will be done using NRI and observed case data.

Ankylosing Spondylitis Disease Activity Score disease activity at Week 48 will also be summarized using descriptive statistics, where counts and percentages are reported for each of the 4 categories. Two summaries will be provided: One will derive disease activity at Week 48 using last observation carried forward (LOCF, impute using the last post-Baseline nonmissing result) for missing values and the other will be based on observed case data.

Change #51

14.3.2.2 Part B analysis

The same logistic regression model as described for the primary efficacy variable will be used to evaluate the noninferiority of CZP 200mg Q4W to CZP 200mg Q2W. Because the 95% CI resulting from the logistic regression model will be based on the odds ratio, a transformation will be necessary so that it can be presented in terms of a percentage difference to evaluate relative to the prespecified noninferiority margin of 15%. The details behind this transformation willbe described in the SAP.

The time to flare will be analyzed using Kaplan-Meier methods. For those who meet the criteria for flare, the time will be defined as the length in days from randomization in Part B until the visit at which the criteria for flare were met. Subjects who discontinue the study without meeting the criteria for flare will be censored at the time of their last study visit. Subjects who complete the study without meeting the criteria for flare will be censored at their Week 96 visit. Between group differences will be analyzed with the log-rank statistic.

The changes from Baseline in ASDAS, BASDAI, BASFI, and BASMI at Week 96 for the FAS will be compared between treatment groups using a mixed model for repeated measures (MMRM).

Has been changed to:

The time to flare will be analyzed using Kaplan-Meier methods. For those who meet the criteria for flare, the time will be defined as the length in days from randomization in Part B until the

visit at which the criteria for flare were met. Subjects who discontinue the study without meeting the criteria for flare will be censored at the time of their last study visit. Subjects who complete the study without meeting the criteria for flare will be censored at their Week 96 visit. Between group differences will be analyzed with the log-rank statistic.

The changes from Baseline in ASDAS, BASDAI, BASFI, and BASMI at Week 96 for the RS will be compared between treatment groups using a mixed model for repeated measures (MMRM).

Change #52

14.3.2.3 Part B analysis for subjects who experience a flare

For subjects who experience a flare during Part B, the secondary efficacy variables listed below will be analyzed. The timepoint for these secondary efficacy analyses will be Week 96 (or later, if applicable, depending on when the flare occurred.

For the continuous variables (ASDAS, BASDAI, BASFI, BASMI), quantitative descriptive statistics by treatment group will be displayed. This summary will include the actual results at Week 96 (or later), change from Baseline (Week 0), change from randomization Baseline (Week 48), and change from the visit in which the flare occurred.

All Part B summaries after subjects experience a flare will be based on observed case data and will use the RS.

Has been changed to:

For subjects who experience a flare during Part B, the secondary efficacy variables listed below will be analyzed. The timepoint for these secondary efficacy analyses will be at Escape Week 12).

For the continuous variables (ASDAS, BASDAI, BASFI, BASMI), quantitative descriptive statistics by treatment group will be displayed. This summary will include the actual results at Escape Week 12, change from Baseline (Week 0), change from randomization Baseline (Week 48), and change from the visit in which the flare occurred.

All Part B summaries after subjects experience a flare will be based on observed case data and will use the FS.

Change #53

14.3.3 Other efficacy analyses

14.3.3.1 Part A

The other efficacy variables for Part A as outlined in Section 4.1.3.1 will be summarized by visit and treatment group using descriptive statistics for the timepoint itself and for the change from Baseline. This will be done for the OLS using observed case data and with imputation using LOCF.

14.3.3.2 Part B

Treatment group comparisons for both CZP groups 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 with variables of Baseline score, treatment group, region, and mNY

criteria (yes/no) in the model. The treatment differences and corresponding 95% CIs will be calculated based on the adjusted means. Missing values will be imputed using LOCF. This analysis approach will be used for the following variables:

- Total and nocturnal spinal pain
- PtGADA
- BASFI
- Morning stiffness (BASDAI 5 and 6)
- SF-36 PCS, MCS, and physical function domain
- Fatigue NRS
- ASQoL

Such analyses will also be done for the following continuous variables: ASDAS, BASDAI, BASFI, and BASMI for timepoints not specified in the secondary efficacy analyses using the same analysis methods described in Section 14.3.2.2. Additionally, ASDAS-MI, ASDAS-CII, and ASAS response variables will be analyzed using a logistic regression model similar to the one specified for binary response variables in Section 14.3.2.2 at timepoints not covered in the secondary efficacy analyses.

Has been changed to:

14.3.3 Other efficacy analyses

14.3.3.1 Part A

The other efficacy variables for Part A as outlined in Section 4.1.3.1 will be summarized by visit using descriptive statistics for the timepoint itself and for the change from Baseline. This will be done for the OLS using observed case data and with imputation using LOCF. Further details are described in the SAP.

14.3.3.2 Part B analysis for subjects who experience a flare

Treatment group comparisons for both CZP groups 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 with variables of Baseline score, treatment group, region, and mNY criteria (yes/no) in the model. The treatment differences and corresponding 95% CIs will be calculated based on the adjusted means. Missing values will be imputed using LOCF. This analysis approach will be used for the following variables:

- Total spinal pain
- Nocturnal spinal pain
- PtGADA
- Morning stiffness (BASDAI 5 and 6)
- SF-36 PCS, MCS, and physical function domain
- Fatigue NRS

- ASQoL

Such analyses will also be done for the following continuous variables: ASDAS, BASDAI, BASFI, and BASMI will be analyzed using a MMRM similar to the one specified in Section 14.3.2.2. at timepoints not covered in the secondary efficacy analyses. Additionally, ASDAS-MI, ASDAS-CII, ASAS, and BASDAI50 response variables will be analyzed using a logistic regression model similar to the one specified for binary response variables in Section 14.3.2.2 at timepoints not covered in the secondary efficacy analyses.

Inserted section 14.3.3.3, Part B analysis for subjects who experience a flare

The other efficacy variables for subjects who experience a flare in Part B as outlined in Section 4.1.3.3 will be summarized by visit and randomized treatment group using descriptive statistics for the timepoint itself and for the change from Baseline. A subset of variables will summarize the change from randomization Baseline (Week 48) and the change from the visit at which the flare occurred. This will be done for the FS using observed case data.

Change #54

14.4.1 Safety analyses

The frequency of all AEs by study period (Part A and Part B) 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 by 100 patient years.

Has been changed to:

The frequency of all AEs by study period (Part A and Part B) will be presented separately by System Organ Class, high-level term, and preferred term and for Part B by each treatment group. 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 by 100 patient years.

Change #55

14.4.2 Pharmacokinetic analysis

Has been changed to:

14.4.2 Pharmacokinetic and immunogenicity analysis

Change #56

14.8 Determination of sample size

It is anticipated that approximately 210 subjects will be randomized in a 1:1:1 ratio to the CZP 200mg Q2W, CZP 200mg Q4W, and placebo treatment groups. The primary efficacy analysis is based on the proportion of subjects who do not experience a flare during Part B of the study. The proportion of subjects who do not experience a flare during Part B is assumed to be 80%, 75%, and 45% for the CZP 200mg Q2W, CZP 200mg Q4W, and placebo treatment groups, respectively. Given these assumptions, a sample size of 70 subjects per group provides 98% power to detect a significant difference between the CZP 200mg Q2W dose and placebo and 94% power to detect a significant difference between the CZP 200mg Q4W dose and placebo using a 2-sided significance level of 0.05. Furthermore, a sample size of 70 subjects per arm

provides 81% power to conclude that the CZP 200mg Q4W dose is noninferior to the CZP 200mg Q2W dose, given a noninferiority margin of 15% and a 1-sided significance level of 0.025.

Has been changed to:

It is anticipated that approximately 210 subjects will be randomized in a 1:1:1 ratio to the CZP 200mg Q2W, CZP 200mg Q4W, and placebo treatment groups. The primary efficacy analysis is based on the proportion of subjects who do not experience a flare during Part B of the study. The proportion of subjects who do not experience a flare during Part B is assumed to be 80%, 75%, and 45% for the CZP 200mg Q2W, CZP 200mg Q4W, and placebo treatment groups, respectively. Given these assumptions, a sample size of 70 subjects per group provides 98% power to detect a significant difference between the CZP 200mg Q2W dose and placebo and 94% power to detect a significant difference between the CZP 200mg Q4W dose and placebo using a 2-sided significance level of 0.05.

Change #57

17 REFERENCES

The following reference was added:

Ware JE, Kosinski M, Bjorner J, Turner-Bowker D, Gandek B, Maruish M. Determining important differences in scores. User's Manual for the SF-36v2® Health Survey. Lincoln (RI): QualityMetric Incorporated; 2007:125-33.

Change #58

18.1 ASAS classification criteria for axSpA

[c] Inflammatory back pain according to ASAS criteria for axSpA defined as the presence of 4 out of 5 of the following parameters:

1) age at onset <40 years

Has been changed to:

[c] Inflammatory back pain according to ASAS criteria for axSpA defined as the presence of 4 out of 5 of the following parameters:

1) age at onset <45 years

18.4 Protocol Amendment 2

Rationale for the amendment

The main purpose of this amendment is to replace references to the current assay for measuring ADAbs in plasma samples (a validated screening 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 AS0005 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.

Moreover, one exclusion criterion (#28) was amended regarding one specific subcriterion: In the original version of the protocol, there was a differentiation of allowed Liver function test (LFT) values in patients with regard to concomitant MTX treatment (Liver function tests exclusionary if >2.0 x ULN for subjects treated with MTX and >ULN in subjects on concomitant MTX treatment). In line with other recent CZP protocols, this was now aligned that LFT >2.0 x ULN are exclusionary for all patients. During enrollment for the study, this was already handled in this way in specifically discussed cases.

In line with the Statistical Analysis Plan (SAP) of the study, the Safety Set Part B (SSB) was added.

In addition, the wording of one inclusion criterion and of some other descriptional details was modified for clarity and solving inconsistencies; current naming conventions were updated and typographical errors corrected.

Specific modifications and changesChange #1

Study contact information

Clinical Project Manager

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Clinical Trial Biostatistician

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Has been changed to:

Clinical Project Manager

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Clinical Trial Biostatistician

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Address:	8010 Arco Corporate Drive Raleigh, NC 27617, USA
Phone:	[redacted]
Fax:	

Change #2

List of abbreviation

The following abbreviations were added:

NAb	Neutralizing antibody
PS	Patient Safety
SSB	Safety Set Part B

The following abbreviation was deleted:

DS	Drug Safety

Change #3

4.2.2 Biomarkers

Selected samples collected for measurement of CZP plasma concentration may be used additionally for analyses of the following biomarkers and cytokines: Matrix metalloproteinase-3 (MMP-3); bone morphogenic protein (BMP) BMP-2, -4 and -7, wingless-related mouse mammary tumor virus integration site protein (WNT1), Inducible Signaling Pathway proteins

(WISP), Gremlin, Dickkopf-related protein 1 (DKK1), Sclerostin, Hedgehog proteins (Shh, Ihh, Dhh), Collagen turnover/cleavage products, collagen type X, vascular endothelial growth factor (VEGF), citrullinated vimentin fragments, cytokines: IL13, IL17 A and F, IL23, IL34, Transforming Growth Factor (TGF)β, Macrophage colony-stimulating factors (M-CSF), Granulocyte macrophage colony-stimulating factor (GM-CSF, CSF-1, soluble CSF-1 Receptor (sCSF1r) levels.

Has been changed to:

Selected samples collected for measurement of CZP plasma concentration may be used additionally for analyses of biomarkers and cytokines. These analyses may include, but are not limited to: Matrix metalloproteinase-3 (MMP-3); bone morphogenic protein (BMP) BMP-2, -4 and -7, wingless-related mouse mammary tumor virus integration site protein (WNT1), Inducible Signaling Pathway proteins (WISP), Gremlin, Dickkopf-related protein 1 (DKK1), Sclerostin, Hedgehog proteins (Shh, Ihh, Dhh), Collagen turnover/cleavage products, collagen type X, vascular endothelial growth factor (VEGF), citrullinated vimentin fragments, cytokines: IL13, IL17 A and F, IL23, IL34, Transforming Growth Factor (TGF)β, Macrophage colony-stimulating factors (M-CSF), Granulocyte macrophage colony-stimulating factor (GM-CSF, CSF-1, soluble CSF-1 Receptor (sCSF1r) levels.

Change #4

4.2.3 Pharmacogenetic variables

Blood samples will be drawn for possible genetic, genomic, and proteomic analysis at Baseline, and, for genomic and proteomics analysis only, additionally at Weeks 12, 24, 48, 72, and 96/WD to enable exploratory evaluation of biomarkers relative to drug treatment and inflammatory and immune response processes. The samples will be stored at -80°C at the Central Laboratory facilities for up to 20 years or according to local laws.

Has been changed to:

Blood samples will be drawn for possible genetic, genomic, and proteomic analysis at Baseline, and, for genomic and proteomics analysis only, additionally at Weeks 12, 24, 48, 72, and 96/WD to enable exploratory evaluation of biomarkers relative to drug treatment and inflammatory and immune response processes. The samples will be stored at -80°C at the Biorepository for up to 20 years or according to local laws.

Change #5

4.3 Immunogenicity variables

Anti-CZP antibody (ADAb) levels will be assessed at Baseline and subsequent timepoints as described in Table 5.1 and Table 5.2.

The number and percent of subjects with ADAb levels above 2.4units/mL will be reported as follows:

- Number and % of subjects with ADAb >2.4units/mL at the time of each visit
- Number and % of subjects with ADAb >2.4units/mL at any visit during treatment (not including posttreatment withdrawal or follow-up visits)

- Number and % of subjects with ADAb >2.4units/mL at any visit including posttreatment withdrawal or follow-up visits

For the subgroup of subjects with at least 1 ADAb >2.4units/mL, the timepoint of occurrence of the first finding will also be displayed.

Has been changed to:

Anti-CZP antibody (ADAb) levels will be assessed at Baseline and subsequent timepoints as described in Table 5.1 and Table 5.2.

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

Change #6

5.2 Schedule of study assessments, Table 5.1

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Week (W) / **Protocol Activity**	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU[b]**
Inclusion/exclusion	X	X																								
Informed consent [c]	X																									
Demographic data	X																									
Medical history (including axSpA and extra-articular manifestations history)	X																									
Vital signs [d]	X	X	X	X		X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X
Hematology/urine/ biochemistry	X[e]	X				X		X		X		X		X					X		X		X		X	X
CRP [f]	X	X	X	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	
Pregnancy testing [g]	X	X																							X	X
PE [h]	X	X				X		X				X			X				X		X		X		X	X
Extra-articular assessments	X	X		X		X		X				X			X		X		X		X		X		X	
Chest x-ray [i]	X																									
TB test [j]	X														X										X	
TB questionnaire	X	X				X		X				X			X				X		X		X		X	
Sacroiliac joint x-	X																									

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Week (W)	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU[b]**
Protocol Activity																										
ray [k]																										
MRI [l]	X														X										X	
Stool sample [m]		X													X										X	
Serum calprotectin		X				X		X						X							X				X	
IBD-Questionnaire		X												X											X	
BASMI and Spinal mobility [n]	X	X	X	X		X		X				X			X		X		X		X		X		X	
BASDAI [f]	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	
SF-36		X		X		X		X				X		X					X		X		X		X	
AsQoL		X	X	X		X		X				X		X					X		X		X		X	
EQ-5D		X				X		X				X		X					X		X		X		X	
MASES		X				X		X				X			X				X		X		X		X	
Total and nocturnal spinal pain		X	X	X		X		X				X		X			X		X		X		X		X	
Swollen and tender joint counts		X	X	X		X		X				X			X		X		X		X		X		X	
Patient's Global Assessment of Disease Activity [f]	X	X	X	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	
Physician's Global Assessment of		X				X		X				X			X		X		X		X		X		X	

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Week (W)	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU[b]**
Protocol Activity																										
Disease Activity																										
Work Productivity Survey		X		X		X		X				X			X				X		X		X		X	
Resources utilization [o]		X				X		X				X			X				X		X		X		X	
CZP plasma concentration/ ADAb		X		X		X		X						X					X		X		X		X	X
Biomarker		X		X		X		X						X					X		X		X		X	X
Genetics		X												X												
Genomics/ proteomics		X				X		X						X							X				X	
Prior and Concomitant medication[p]	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
IXRS	X	X	X	X		X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X
Study drug sc onsite		X	X	X		X		X		X		X			X		X		X		X		X			
Study drug sc self-inj. at home					X		X		X		X		X													
Randomization															X											

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A													PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**												**3 (Double-Blind)**											**4**
Week (W) / **Protocol Activity**	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU [b]**
Nurse visit at subj. home (incl. study drug sc inj.) [q]																X		X		X		X		X		
Check of sustained remission criteria [r]						X		X		X		X			X	X	X	X	X	X	X	X	X	X		
Telephone Contact [s]					X		X		X				X													

Abs=antibodies; ADAb= anti-CZP antibody concentration; AEs=adverse events; AS=ankylosing spondylitis; AsQoL=Ankylosing Spondylitis Quality of Life; axSpA=axial spondyloarthritis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; CZP=certolizumab pegol; EQ-5D=EuroQoL Health Status Questionnaire; H=home, no site visit; HIV=human immunodeficiency virus; HLA-B27=human leukocyte antigen B27; HN=home nurse visit at subject's home; IBD=Inflammatory bowel disease; incl.=including; inj=injection; IXRS=Interactive Voice or Web Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MRI=magnetic resonance imaging; PE=physical exam; sc=subcutaneously; SF-36=Short‑Form 36‑item Health Survey; SFU=Safety Follow-Up; SI=sacroiliac; subj=subject; TB=tuberculosis; W=Week; WD=Withdrawal; WHO=World Health Organization

[a] Assessments conducted 3 to 5 days prior to Week 48 will serve as the qualification assessments for subjects determined to be eligible for randomization into Part B at Week 48.

[b] SFU: 10 weeks after last dose of study medication.

[c] 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 be obtained from subjects consenting also to the use of their blood samples for possible genetic, genomic, and proteomic analysis.

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

[e] Testing to rule out hepatitis B surface antigen, antibodies to hepatitis C, antibodies to HIV and HLA-B27 at Screening only.

[f] To be assessed as indicated and from Week 52 onwards every 4 weeks only.

[g] Pregnancy testing for women of childbearing potential will be serum testing at the Screening Visit and SFU and urine testing at Baseline and Week 96/WD Visit.

[h] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Weight is to be measured at Screening, Baseline, Week 48, and at Week 96/WD. Height will be measured at the Baseline Visit only.

[i] Screening chest x-ray must have occurred within 3 months prior to Screening Visit and should be repeated only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure).

[j] QuantiFERON TB GOLD test or another WHO-validated IGRA test such as Elispot test, if QuantiFERON TB GOLD test is not locally available. The TB test will be repeated at Week 48 and 96 (or at WD Visit if medically indicated) for subjects with previously negative TB test result.

[k] Sacroiliac joint x-rays will be performed at Screening and used as the Baseline assessment for all subjects. An SIJ x-ray performed ≤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.

[l] Magnetic resonance imaging of the spine and sacroiliac joints to be performed at Screening, Week 48, and 96 or WD Visit if MRI was performed more than 12 weeks prior to WD Visit.

[m] Kit for collection of stool sample to be provided at Screening Visit. Stool sample shall be obtained prior to Baseline and provided to the Investigator at the Baseline Visit.

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

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

[p] Prior medication will be at Screening only.

[q] Nurse visit at home only where approved and with agreement of subjects. Otherwise, the visit procedures will be done onsite by the site staff.

[r] Refer to Protocol Section 3 for definition. In case of loss of sustained remission in Part B, the subject must visit the study site for the next scheduled dose of study medication. The Investigator will initiate the escape treatment as appropriate. Refer to Table 5.2 for details.

[s] Subjects will be contacted by telephone about every 4 weeks in between the onsite visits

Has been changed to:

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Week (W) **Protocol Activity**	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU[b]**
Inclusion/exclusion	X	X																								
Informed consent [c]	X																									
Demographic data	X																									
Medical history (including axSpA and extra-articular manifestations history)	X																									
Vital signs [d]	X	X	X	X		X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X
Hematology/urine/ biochemistry	X[e]	X				X		X		X		X		X					X		X		X		X	X
CRP [f]	X	X	X	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	
Pregnancy testing [g]	X	X																							X	X
PE [h]	X	X				X		X				X			X				X		X		X		X	X
Extra-articular assessments		X		X		X		X				X			X		X		X		X		X		X	
Chest x-ray [i]	X																									
TB test [j]	X														X										X	
TB questionnaire	X	X				X		X				X			X				X		X		X		X	
Sacroiliac joint x-	X																									

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Week (W)	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU[b]**
Protocol Activity																										
ray [k]																										
MRI [l]	X														X										X	
Stool sample [m]		X													X										X	
Serum calprotectin		X				X		X						X							X				X	
IBD-Questionnaire		X												X											X	
BASMI and Spinal mobility [n]	X	X	X	X		X		X				X			X		X		X		X		X		X	
BASDAI [f]	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	
SF-36		X		X		X		X				X		X					X		X		X		X	
AsQoL		X	X	X		X		X				X		X					X		X		X		X	
EQ-5D		X				X		X				X		X					X		X		X		X	
MASES		X				X		X				X			X				X		X		X		X	
Total and nocturnal spinal pain		X	X	X		X		X				X		X			X		X		X		X		X	
Swollen and tender joint counts		X	X	X		X		X				X			X		X		X		X		X		X	
Patient's Global Assessment of Disease Activity [f]	X	X	X	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	
Physician's Global Assessment of		X				X		X				X			X		X		X		X		X		X	

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Week (W)	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU[b]**
Protocol Activity																										
Disease Activity																										
Work Productivity Survey		X		X		X		X				X			X				X		X		X		X	
Resources utilization [o]		X				X		X				X			X				X		X		X		X	
CZP plasma concentration/ ADAb		X		X		X		X						X					X		X		X		X	X
Biomarker		X		X		X		X						X					X		X		X		X	X
Genetics		X												X												
Genomics/ proteomics		X				X		X						X							X				X	
Prior and Concomitant medication[p]	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
IXRS	X	X	X	X		X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X
Study drug sc onsite		X	X	X		X		X		X		X			X		X		X		X		X			
Study drug sc self-inj. at home					X		X		X		X		X													
Randomization															X											

Table 5.1: Schedule of study assessments for all subjects completing Part A and Part B

	PART A														PART B											
Study Period	**1 (Screening)**	**2 (Open-Label)**													**3 (Double-Blind)**											**4**
Week (W) / **Protocol Activity**	**-5 to -1 weeks**	**0**	**2**	**4**	**6 to 10 H**	**12**	**14 to 22 H**	**24**	**26 to 30 H**	**32**	**34 H**	**36**	**38 to 46 H**	**3-5 days prior to W48 visit[a]**	**48**	**50 HN**	**52**	**54 to 58 HN**	**60**	**62 to 70 HN**	**72**	**74 to 82 HN**	**84**	**86 to 94 HN**	**96/ WD**	**SFU [b]**
Nurse visit at subj. home (incl. study drug sc inj.) [q]																X		X		X		X		X		
Check of sustained remission criteria [r]						X		X		X		X			X	X	X	X	X	X	X	X	X	X		
Telephone Contact [s]					X		X		X				X													

Abs=antibodies; ADAb=anti-CZP antibody; AEs=adverse events; AS=ankylosing spondylitis; AsQoL=Ankylosing Spondylitis Quality of Life; axSpA=axial spondyloarthritis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; CZP=certolizumab pegol; EQ-5D=EuroQoL Health Status Questionnaire; H=home, no site visit; HIV=human immunodeficiency virus; HLA-B27=human leukocyte antigen B27; HN=home nurse visit at subject's home; IBD=Inflammatory bowel disease; incl.=including; inj=injection; IXRS=Interactive Voice or Web Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MRI=magnetic resonance imaging; PE=physical exam; sc=subcutaneously; SF-36=Short-Form 36-item Health Survey; SFU=Safety Follow-Up; SI=sacroiliac; subj=subject; TB=tuberculosis; W=Week; WD=Withdrawal; WHO=World Health Organization

[a] Assessments conducted 3 to 5 days prior to Week 48 will serve as the qualification assessments for subjects determined to be eligible for randomization into Part B at Week 48.

[b] SFU: 10 weeks after last dose of study medication.

[c] 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 be obtained from subjects consenting also to the use of their blood samples for possible genetic, genomic, and proteomic analysis.

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

[e] Testing to rule out hepatitis B surface antigen, antibodies to hepatitis C, antibodies to HIV and HLA-B27 at Screening only.

[f] To be assessed as indicated and from Week 52 onwards every 4 weeks only.

[g] Pregnancy testing for women of childbearing potential will be serum testing at the Screening Visit and SFU and urine testing at Baseline and Week 96/WD Visit.

[h] Includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB. Weight is to be measured at Screening, Baseline, Week 48, and at Week 96/WD. Height will be measured at the Baseline Visit only.

[i] Screening chest x-ray must have occurred within 3 months prior to Screening or during Screening, and should be repeated only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure).
[j] QuantiFERON TB GOLD test or another WHO-validated IGRA test such as Elispot test, if QuantiFERON TB GOLD test is not locally available. The TB test will be repeated at Week 48 and 96 (or at WD Visit if medically indicated) for subjects with previously negative TB test result.
[k] Sacroiliac joint x-rays will be performed at Screening and used as the Baseline assessment for all subjects. An SIJ x-ray performed ≤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.
[l] Magnetic resonance imaging of the spine and sacroiliac joints to be performed at Screening, and within a ± 2 weeks time window at Weeks 48 and 96 or WD Visit if MRI was performed more than 12 weeks prior to WD Visit.
[m] Kit for collection of stool sample to be provided at Screening Visit. Stool sample shall be obtained prior to Baseline and provided to the Investigator at the Baseline Visit.
[n] Occiput to wall distance; chest expansion; and BASMI, which includes modified Schober test, lateral spinal flexion, cervical rotation, tragus to wall distance, and maximal intermalleolar distance.
[o] Resource utilization includes: concomitant medical procedures, health care provider consultations not foreseen by the protocol, hospitalizations/emergency room visits.
[p] Prior medication will be at Screening only.
[q] Nurse visit at home only where approved and with agreement of subjects. Otherwise, the visit procedures will be done onsite by the site staff.
[r] Refer to Protocol Section 3 for definition. In case of loss of sustained remission in Part B, the subject must visit the study site for the next scheduled dose of study medication. The Investigator will initiate the escape treatment as appropriate. Refer to Table 5.2 for details.
[s] Subjects will be contacted by telephone about every 4 weeks in between the onsite visits.

Change #7

5.2 Schedule of study assessments, Table 5.2

Table 5.2: Schedule of study assessments for all subjects experiencing a flare in Part B

	Part B for subjects experiencing a flare					
Study-Period	**3B**					
Visit / week (W) on escape treatment	**0**	**2**	**4**	**6 to 10 H/HN [a]**	**12 (and every 12 weeks thereafter) [b]**	**every 2 weeks in between [c] H/HN [a]**
Protocol Activity						
Vital signs [d]	X	X	X		X	
Hematology/urine/ biochemistry	X				X	
CRP [e]	X	X	X	X [f]	X	X [f]
Stool sample [g]	X				X	
Serum calprotectin [g]	X				X	
IBD-Questionnaire [g]	X				X	
PE	X	X	X		X	
Extra-articular assessments	X		X		X	
MRI [h]	X				X	
TB questionnaire	X				X	
BASMI & Spinal mobility [i]	X	X	X		X	
BASDAI	X	X	X	X [f]	X	X [f]
BASFI	X	X	X		X	
SF-36	X		X		X	
AsQoL	X	X	X		X	
EQ-5D	X		X		X	
MASES	X	X	X		X	
Total and nocturnal spinal pain	X	X	X		X	
Patient's Global Assessment of Disease Activity	X	X	X	X [f]	X	X [f]
Physician's Global Assessment of Disease Activity	X	X	X		X	
Work Productivity Survey	X		X		X	
Resources utilization [j]	X		X		X	
CZP plasma concentration/ADAb	X	X	X		X	
Biomarker	X	X	X		X	

Table 5.2: Schedule of study assessments for all subjects experiencing a flare in Part B

	Part B for subjects experiencing a flare					
Study-Period	**3B**					
Visit / week (W) on escape treatment	**0**	**2**	**4**	**6 to 10 H/HN [a]**	**12 (and every 12 weeks thereafter) [b]**	**every 2 weeks in between [c] H/HN [a]**
Protocol Activity						
Concomitant medication	X	X	X		X	
AEs	X	X	X		X	
IXRS	X	X	X	X	X	X
Study drug sc onsite	X	X	X		X	
Study drug sc self-inj. at home				X		X
Telephone Contact [k]				X		X

Abs=antibodies; ADAb=anti-CZP antibody concentration; AEs=adverse events; AS=ankylosing spondylitis; AsQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; CZP=certolizumab pegol; EQ-5D=EuroQoL Health Status Questionnaire; H=home, no site visit; HN=home nurse visit at subjects home; IBD=Inflammatory bowel disease; IXRS=Interactive Voice or Web Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MRI=magnetic resonance imaging; PE=physical exam; sc=subcutaneously; SF-36=Short-Form 36-item Health Survey; TB=tuberculosis; W=Week

[a] HN Q4W only for obtaining blood sample (CRP) and electronic patient reported outcome (ePRO) data as indicated

[b] Schedule onsite visit every 12 weeks until Week 96 of regular visit schedule is reached. For example, at Weeks 74 and 86, if start of escape treatment is at Week 62 (=Escape Week 0). At Week 96 and SFU, perform assessments as described in Table 5.1. For subjects experiencing a flare at/after Week 82, escape treatment should be provided for 12 weeks and the subject invited for the final assessment visit (as laid down for Week 96) 2 weeks later

[c] Until 2 weeks before Week 96 of regular visit schedule is reached

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

[e] To be assessed as indicated and from Week 52 onwards every 4 weeks only

[f] To be assessed every 4 weeks only

[g] To be assessed at escape Weeks 0 and 12 only

[h] To be performed at escape Weeks 0 and 12 only and at final assessment visit at Week 96, if the last MRI was done at least 12 weeks prior to Week 96

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

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

[k] Subjects will be contacted by telephone about every 4 weeks in between the onsite visits

Has been changed to:

Table 5.2: Schedule of study assessments for all subjects experiencing a flare in Part B

	Part B for subjects experiencing a flare					
Study-Period	**3B**					
Visit / week (W) on escape treatment	**0**	**2**	**4**	**6 to 10 H/HN [a]**	**12 (and every 12 weeks thereafter) [b]**	**every 2 weeks in between [c] H/HN [a]**
Protocol Activity						
Vital signs [d]	X	X	X		X	
Hematology/urine/ biochemistry	X				X	
CRP [e]	X	X	X	X [f]	X	X [f]
Stool sample [g]	X				X	
Serum calprotectin [g]	X				X	
IBD-Questionnaire [g]	X				X	
PE	X	X	X		X	
Extra-articular assessments	X		X		X	
MRI [h]	X				X	
TB questionnaire	X				X	
BASMI & Spinal mobility [i]	X	X	X		X	
BASDAI	X	X	X	X [f]	X	X [f]
BASFI	X	X	X		X	
SF-36	X		X		X	
AsQoL	X	X	X		X	
EQ-5D	X		X		X	
MASES	X	X	X		X	
Total and nocturnal spinal pain	X	X	X		X	
Patient's Global Assessment of Disease Activity	X	X	X	X [f]	X	X [f]
Physician's Global Assessment of Disease Activity	X	X	X		X	
Work Productivity Survey	X		X		X	
Resources utilization [j]	X		X		X	
CZP plasma concentration/ADA	X	X	X		X	
Biomarker	X	X	X		X	
Concomitant medication	X	X	X		X	

Table 5.2: Schedule of study assessments for all subjects experiencing a flare in Part B

	Part B for subjects experiencing a flare					
Study-Period	**3B**					
Visit / week (W) on escape treatment	**0**	**2**	**4**	**6 to 10 H/HN [a]**	**12 (and every 12 weeks thereafter) [b]**	**every 2 weeks in between [c] H/HN [a]**
Protocol Activity						
AEs	X	X	X		X	
IXRS	X	X	X	X	X	X
Study drug sc onsite	X	X	X		X	
Study drug sc self-inj. at home				X		X
Telephone Contact [k]				X		X

Abs=antibodies; ADAb=anti-CZP antibody; AEs=adverse events; AS=ankylosing spondylitis; AsQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; CZP=certolizumab pegol; EQ-5D=EuroQoL Health Status Questionnaire; H=home, no site visit; HN=home nurse visit at subjects home; IBD=Inflammatory bowel disease; IXRS=Interactive Voice or Web Response System; MASES=Maastricht Ankylosis Spondylitis Enthesitis Score; MRI=magnetic resonance imaging; PE=physical exam; sc=subcutaneously; SF-36=Short-Form 36-item Health Survey; TB=tuberculosis; W=Week

[a] HN Q4W only for obtaining blood sample (CRP) and electronic patient reported outcome (ePRO) data as indicated

[b] Schedule onsite visit every 12 weeks until Week 96 of regular visit schedule is reached. For example, at Weeks 74 and 86, if start of escape treatment is at Week 62 (=Escape Week 0). At Week 96 and SFU, perform assessments as described in Table 5.1. For subjects experiencing a flare at/after Week 82, escape treatment should be provided for 12 weeks and the subject invited for the final assessment visit (as laid down for Week 96) 2 weeks later

[c] Until 2 weeks before Week 96 of regular visit schedule is reached

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

[e] To be assessed as indicated and from Week 52 onwards every 4 weeks only

[f] To be assessed every 4 weeks only (Week 8, 12, 16, 20, 24, … up to Week 96)

[g] To be assessed at escape Weeks 0 and 12 only

[h] To be performed at escape Weeks 0 and 12 only and at final assessment visit at Week 96, if the last MRI was done at least 12 weeks prior to Week 96. Magnetic resonance imaging is to be performed within a ±2-weeks time window.

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

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

[k] Subjects will be contacted by telephone about every 4 weeks in between the onsite visits

Change #8

Section 6.1 Inclusion criteria, inclusion criterion 5

5. Subjects must have a documented diagnosis of adult-onset axSpA with at least 3 months' symptom duration as defined by the specified ASAS criteria (according to Appendix 18.1) and symptom duration of less than 5 years prior to the participation of this study.

Has been changed to:

5. Subjects must have a documented diagnosis of adult-onset axSpA with at least 3 months' symptom duration and meet the ASAS classification criteria for axSpA (according to Appendix 18.1) and symptom duration of less than 5 years prior to the participation of this study.

Change #9

6.2 Exclusion criteria, criterion 28

28. Subjects with significant laboratory abnormalities included but not limited to:

- Liver function tests >2.0 x ULN, if the subject is not treated with MTX and >ULN if subject is on concomitant MTX treatment
- Estimated Glomerular Filtration Rate (GFR) as measured by Chronic Kidney Disease Epidemiology Collaboration (Levey et al, 2009) <60 mL/min/1.73m^2
- White blood cell (WBC) <3.0x10^9/L.

Has been changed to:

28. Subjects with significant laboratory abnormalities included but not limited to:

- Liver function tests >2.0 x ULN
- Estimated Glomerular Filtration Rate (GFR) as measured by Chronic Kidney Disease Epidemiology Collaboration (Levey et al, 2009) <60 mL/min/1.73m^2
- Wite blood cell (WBC) <3.0x10^9/L

Change #10

7.9 Blinding (first paragraph)

Due to differences in presentation and viscosity between active and placebo, special precautions will be taken in order to ensure blinding of the study during Part B. The subject will receive the IMP throughout the study duration for each single administration in a sealed box with a 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 of the study (CZP 200mg or placebo). Administration of the IMP will be done according to the schedule of study assessments (Table 5.1) either onsite by appropriately trained unblinded study personnel or at home by the unblinded home nurse. C-reactive protein, PK, and antibody data will be provided only after the study is unblinded.

[…]

Has been changed to:

Due to differences in presentation and viscosity between active and placebo, special precautions will be taken in order to ensure blinding of the study during Part B. The subject will receive the IMP throughout the study duration for each single administration in a sealed box with a 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 of the study (CZP 200mg or placebo). Administration of the IMP will be done according to the schedule of study assessments (Table 5.1) either onsite by appropriately trained unblinded study personnel or at home by the unblinded home nurse.

[…]

Change #11

8 **Study procedures by visit**

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

During the study, the Investigator will assess each subject over the entire study period of up to 109 weeks including a SFU Period of 10 weeks after the last dose. Visit windows of ±3 days on either side of the scheduled dosing are permitted; however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±3 days is relative to Baseline and 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:

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

During the study, the Investigator will assess each subject over the entire study period of up to 109 weeks including a SFU Period of 10 weeks after the last dose. Visit windows of ±3 days on either side of the scheduled dosing are permitted; however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±3 days is relative to Baseline and 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. For the conduct of MRI, the acceptable time window is ±2 weeks.

Change #12

8.1 Screening Visit (up to 5 weeks)

[…]

- Physical examination (including weight, evaluation of signs and symptoms of active TB and risk factors for exposure to TB) and extra-articular assessment

[…]

Has been changed to:

[…]

- Physical examination (including weight, evaluation of signs and symptoms of active TB and risk factors for exposure to TB)

[…]

Change #13

9.1.4 MRI assessments

Magnetic resonance imaging of the spine and sacroiliac joints will be performed at Screening, Week 48, Week 96, or WD Visit if MRI was performed more than 12 weeks prior to WD. Magnetic resonance imaging 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 sacroiliac joints will be performed at Screening, Week 48, Week 96, or WD Visit if MRI was performed more than 12 weeks prior to WD. Magnetic resonance imaging 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. In addition, a single reader assessment will be performed for change from Baseline (Week 48) evaluation in sacroiliac SPARCC and ASspIMRI-a in the Berlin-modification scores for all subjects that entered Part A.

Change #14

10 Assessment of pharmacokinetics and pharmacogenomic variables

Plasma samples for the measurement of CZP concentrations will be taken at Baseline and Weeks 4, 12, 24, 48, 60, 72, 84, 96/WD, and at the SFU visit 10 weeks after the last dose of study medication. For escapers plasma samples will be taken after the flare at Escape Weeks 0, 2, 4, 12, and further every 12 weeks until Week 96/WD (refer to Table 5.2 for details). 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.

Plasma samples for possible analyses of exploratory biomarkers will be taken at Baseline and Weeks 4, 12, 24, 48, 60, 72, 84, 96/WD, and at the SFU visit 10 weeks after the last dose of study medication. For escapers plasma samples will be taken after the flare at Escape Weeks 0, 2, 4, 12, and further every 12 weeks until Week 96/WD (refer to Table 5.2 for details). Selected biomarkers that may be analyzed are: MMP-3; BMP-2, -4, and -7, WNT1, WISP, Gremlin, DKK1, Sclerostin, Hedgehog proteins (Shh, Ihh, Dhh), Collagen turnover/cleavage products, collagen type X, VEGF, citrullinated vimentin fragments, cytokines: IL13, IL17 A and F, IL23, IL34, TGF-β, M-CSF, GM-CSF, CSF-1, sCSF1r levels.

[…]

Has been changed to:

Plasma samples for the measurement of CZP concentrations will be taken at Baseline and Weeks 4, 12, 24, 3 to 5 days prior to Week 48, and Weeks 60, 72, 84, 96/WD, and at the SFU visit 10 weeks after the last dose of study medication. For escapers plasma samples will be taken after the flare at Escape Weeks 0, 2, 4, 12, and further every 12 weeks until Week 96/WD (refer to Table 5.2 for details). 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.

Plasma samples for possible analyses of exploratory biomarkers will be taken at Baseline and Weeks 4, 12, 24, 3 to 5 days prior to Week 48, and Weeks 60, 72, 84, 96/WD, and at the SFU visit 10 weeks after the last dose of study medication. For escapers plasma samples will be taken after the flare at Escape Weeks 0, 2, 4, 12, and further every 12 weeks until Week 96/WD (refer to Table 5.2 for details). Selected biomarkers that may be analyzed are: MMP-3; BMP-2, -4, and -7, WNT1, WISP, Gremlin, DKK1, Sclerostin, Hedgehog proteins (Shh, Ihh, Dhh), Collagen turnover/cleavage products, collagen type X, VEGF, citrullinated vimentin fragments, cytokines: IL13, IL17 A and F, IL23, IL34, TGF-β, M-CSF, GM-CSF, CSF-1, sCSF1r levels.

[…]

Change #15

11 **Assessment of immunogenicity variables**

Plasma samples for the measurement of ADAb levels will be taken at Baseline (Week 0) and Weeks 4, 12, 24, 48, 60, 72, 84, 96, and the SFU visit (10 weeks after the last dose of study medication). For escapers plasma samples will be taken after the flare at Escape Weeks 0, 2, 4, 12, and further every 12 weeks until Week 96/WD (refer to Tabke 5.2 for details). The number and percent of subjects with ADAb levels above 2.4units/mL will be reported as follows:

- At the time of each visit
- At any visit during treatment (not including posttreatment withdrawal or follow-up visits)
- At any visit including posttreatment withdrawal or follow-up 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 ADAb and potentially NAb levels will be taken at Baseline (Week 0) and Weeks 4, 12, 24, 48, 60, 72, 84, 96, and the SFU visit (10 weeks after the last dose of study medication). For escapers, plasma samples will be taken after the flare at Escape Weeks 0, 2, 4, 12, and further every 12 weeks until Week 96/WD (refer to Table 5.2 for details).

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

Change #16

12.6 Laboratory measurements, first sentence

Hematology, biochemistry, and urinalysis samples will be taken at Screening, Baseline (Week 0), Weeks 12, 24, 32, 36, 3 to 5 days prior to 48, and 60, 72, 84, 96/WD, and at the SFU Visit (10 weeks after the last dose).

Has been changed to:

Hematology, biochemistry, and urinalysis samples will be taken at Screening, Baseline (Week 0), Weeks 12, 24, 32, 36, 3 to 5 days prior to Week 48, and Weeks 60, 72, 84, 96/WD, and at the SFU Visit (10 weeks after the last dose).

Change #17

14.1 Definition of analysis sets

The following analysis set has been added:

The Safety Set Part B (SSB) will consist of all subjects in the RS who have received at least 1 dose of study medication in the Double-Blind Period of the study (Part B).

Change #18

14.1 Definition of analysis sets, last sentence

[…]

The Pharmacokinetic Set B (PKSB) will consist of all subjects from the SS who provide at least 1 PK sample during Part B.

Has been changed to:

[…]

The Pharmacokinetic Set B (PKSB) will consist of all subjects from the SSB who provide at least 1 PK sample during Part B.

Change #19

14.2 General statistical considerations

The second test is performed only if the first test is significant at the 0.05 level.

Has been changed to:

The second test will be performed irrespective of whether the first test is significant at the 0.05 level or not. However, the second test will be interpreted as statistically significant only if the first test is significant at the 0.05 level as well.

Change #20

14.3.1 Analysis of the primary efficacy variable, 3rd paragraph

Subgroup analyses based on age, gender, race, region, CRP level, ADAb status (> or ≤2.4 units/mL), and mNY criteria will be performed. These analyses will be done for the primary efficacy variable and will be based on descriptive statistics only.

Has been changed to:

Subgroup analyses based on age, gender, race, region, CRP level, ADAb status, and mNY criteria will be performed. These analyses will be done for the primary efficacy variable and will be based on descriptive statistics only.

Change #21

14.4.1 Safety analyses, last sentence

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

Has been changed to:

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

Change #22

14.4.2 Pharmacokinetic and immunogenicity analysis

Certolizumab pegol plasma concentrations will be tabulated and summarized by treatment group (overall and by ADAb levels within each treatment group) for each visit at which samples were taken using the geometric mean, 95% CI, geometric coefficient of variation, arithmetic mean, arithmetic SD, median, minimum, and maximum. For each treatment group, plasma concentration time curves will be plotted overall and by antibody level (above or below 2.4units/mL).

Subgroup analyses based on age, gender, race, region, CRP level, antibody level, and mNY criteria will be performed. For the subgroup of subjects with at least 1 ADAb level above 2.4units/mL, the timepoint of occurrence of the first finding will also be displayed.

Frequency tables of ADAb level by visit will be presented. In addition, safety and efficacy profiles by ADAb 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, 95% CI, geometric coefficient of variation, arithmetic mean, arithmetic SD, median, minimum, and maximum.

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.

19 DECLARATION AND SIGNATURE OF INVESTIGATOR

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

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

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

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

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

Investigator:

Printed name	Date/Signature

20 SPONSOR DECLARATION

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

as0005-protocol-amend-2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	24-Jan-2018 12:07 GMT+01
	Clinical Approval	24-Jan-2018 13:33 GMT+01
	Clinical Approval	24-Jan-2018 21:07 GMT+01