PROTOCOL AS0007 AMENDMENT 3

MULTICENTER, OPEN-LABEL STUDY TO ASSESS THE EFFECTS OF CERTOLIZUMAB PEGOL ON THE REDUCTION OF ANTERIOR UVEITIS FLARES IN AXIAL SPONDYLOARTHRITIS SUBJECTS WITH A HISTORY OF ANTERIOR UVEITIS (C-VIEW)

PHASE 4

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LIST OF ABBREVIATIONS

ABA	abatacept
ADA	adalimumab
AE	adverse event
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
AU	anterior uveitis
axSpA	axial spondyloarthritis
AZA	azathioprine
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
CD20	cluster of differentiation 20
CDMS	clinical data management system
CI	clinical improvement
CII	clinically important improvement
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
CRO	contract research organization
CRP	C-reactive protein
CZP	certolizumab pegol
DMARD	disease-modifying antirheumatic drug
DS	Drug Safety
ECG	electrocardiogram
eCRF	electronic Case Report Form
ePRO	electronic patient reported outcome
ES	Enrolled Set
ETN	etanercept
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FU	Follow-Up

GCP	Good Clinical Practice
GOL	golimumab
HCQ	hydroxychloroquine
HI	Health Index
HIV	human immunodeficiency virus
HLA-B27	human leukocyte antigen B27
HRQoL	health-related quality of life
ia	intra-articular
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation
ID	inactive disease
IEC	Independent Ethics Committee
IFX	infliximab
IGRA	Interferon-Gamma Release Assay
IMP	investigational medicinal product
IRB	Institutional Review Board
iv	intravenous(ly)
IWRS	interactive web response system
JIA	juvenile idiopathic arthritis
LFN	leflunomide
LTBI	latent tuberculosis infection
MCID	minimal clinically important difference
MI	major improvement
mNY	modified New York (classification criteria)
MRI	magnetic resonance imaging
MTX	methotrexate
nr-axSpA	nonradiographic axSpA
NRS	Numerical Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
PsA	psoriatic arthritis
PEG	polyethylene glycol

PhGADA	Physician's Global Assessment of Disease Activity
PR	partial remission
PtGADA	Patient's Global Assessment of Disease Activity
Q2W	every 2 weeks (every other week)
RA	rheumatoid arthritis
RCT	randomized controlled trial
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SD	standard deviation
SF-36	Short-Form 36-Item Health Survey
SIJ	sacroiliac joint
SOP	Standard Operating Procedure
SpA	spondyloarthritis
SPC	Summary of Product Characteristics
SS	Safety Set
SSZ	sulfasalazine
TB	tuberculosis
TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
WBC	white blood cell
WD	withdrawal
VEGF	vascular endothelial growth factor
VAS	visual analog scale

1 SUMMARY

AS0007 is a multicenter, open-label, Phase 4 study to evaluate the effects of certolizumab pegol (CZP) on the incidence of anterior uveitis (AU) flares per year in subjects with both active axial spondyloarthritis (axSpA) and a history of AU by comparing the historical AU flare rate that occurred prior to CZP treatment with the AU flare rate occurring while under CZP treatment.

Approximately 130 subjects will be screened in Europe in order to enroll 86 subjects into the study.

The study duration from the start of treatment will be 96 weeks from Baseline onwards, and a follow-up visit will be performed at Week 104; 10 weeks after the last dose at Week 94.

The study includes 3 periods as follows:

- **Period 1** (Screening Period): 1 to 5 weeks before Baseline

Subjects will be informed about the study and sign the informed consent form (ICF). Eligibility will be evaluated and assessments will be performed. The Screening Period should be kept as short as possible but can be extended to 5 weeks if certain medications need to be washed out or to allow to obtain information from the subject's ophthalmologist. For subjects who start a prophylactic treatment for latent tuberculosis infection (LTBI) the Screening Period can be extended up to 12 weeks; see Section 10.6.4.1.

- **Period 2** (Treatment Period): Week 0 to Week 96

Eligible subjects will receive a dose of CZP 400mg subcutaneously (sc) at Baseline, Week 2, and Week 4 followed by CZP 200mg sc every 2 weeks (Q2W) starting at Week 6 until Week 94.

All subjects will be trained at the beginning of the study on self-administration before the subjects start self-administration with the study drug (relative or caregiver may also perform the injections). The injection schedule will provide the sequence of self-administration and site visits including injection at the site.

- **Period 3** (Follow-Up [FU] Period): 10 weeks from the final dose of study medication received.

All subjects will have a FU Visit at Week 104 or earlier in case of an early withdrawal (WD), 10 weeks after the final administration of CZP administration received within the study.

A Week 48 analysis will be performed after all subjects have either completed the Week 48 Visit or have prematurely withdrawn prior to the Week 48 Visit. The final analysis will be conducted at the end of the study after all study data is locked.

The primary objective of the study will be to demonstrate the effect of CZP treatment on the reduction of AU flares in subjects with both active axSpA and a documented history of AU. The secondary objectives of the study will be to assess the effect of CZP treatment on 1) the reduction of AU flares in subjects with axSpA having at least 1 documented history of AU within 12 months prior to Baseline and 2) axSpA disease activity. Other objectives and safety objective are listed in Section 3.3 and Section 3.4, respectively.

2 INTRODUCTION

2.1 Natural history of axial spondyloarthritis

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

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

Patients with AS have definitive evidence of structural changes in the SIJ (sacroiliitis) on x-ray, fulfilling the modified NY (mNY) classification criteria (mNY-positive) (van der Linden, 1984); whereas, those with nr-axSpA structural changes on conventional radiographs do not meet the mNY classification criteria (mNY-negative) (Appendix 16.1) (Rudwaleit et al, 2005; Dougados et al, 1991).

In patients with axSpA, the disease typically originates in the SIJs, then progresses to the spine. In the SIJs 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 SIJs 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 C-reactive protein (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 SIJs and may fulfill the mNY classification 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, 2013).

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, 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, 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 Uveitis in axial spondyloarthritis

Uveitis is the third leading cause of blindness in developed countries. The annual incidence rate is estimated between 17 and 52 per 100,000 persons, and the prevalence is 38 to 714 per 100,000 persons (Wakefield and Chang, 2005). Males and females are generally equally affected overall, but sex preponderance may be observed in some uveitis groups, such as a male predominance HLA-B27 associated uveitis and a female preponderance in juvenile idiopathic arthritis (JIA)-related uveitis. Uveitis may occur at any age, but most commonly affects the population aged between 20 and 59 years.

Uveitis is the most common extra-articular manifestation experienced by patients with axSpA (Boonen et al, 2002) and affects patients with both AS and nr-axSpA (Boonen et al, 2003). Although limited information is available regarding the overall axSpA population, 1 study reported the prevalence of ever experiencing a uveitis flare to be 19.3% for AS patients with disease duration of ≤5 years and 12.4% for nr-axSpA patients (Braun et al, 2006). Reports from patients with established AS suggest that approximately 40% of patients will experience 1 or more uveitis flares during the course of their disease (Braun and Sieper, 2007), and observational data sources (such as cohort studies and patient registries) have reported that 10% to 30% of axSpA patients classified using the ASAS criteria have a history of uveitis (Boonen et al 2003, Braun et al, 2011). Moreover, an attack of acute AU can be the first presenting symptom that leads to a diagnosis of axSpA (Braun, 2012).

The burden of uveitis on affected patients is high, as it is commonly associated with photophobia, pain, and in some cases blurred vision (Braun, 2012). In axSpA patients, AU can range from a single flare to an episodic and recurrent course. Flares of uveitis are typically of sudden onset in a unilateral fashion (Callhoff et al, 2015). Regardless of disease course, in patients developing uveitis, impaired visual performance and reduced health-related quality of life is reported (Cantini et al, 2013). Acute attacks usually resolve completely with topical corticosteroid treatment. For axSpA patients who develop episodic and recurrent uveitis flares, treatment is limited. Nonsteriodal anti-inflammatory drugs (NSAIDs) may relieve symptoms for a short period of time (Cuirea et al, 2013), and the disease-modifying antirheumatic drugs (DMARDs) sulfasalazine (SSZ) and methotrexate (MTX) have been used, although available evidence relating to a possible decrease in flares of uveitis is limited to observational reports (Dougados et al, 1991; Dougados et al, 2013; Feldtkeller et al, 2000: Haibel et al, 2005). Given the lack of treatment options and the fact that a substantial proportion of axSpA patients are resistant to conventional therapies, new treatment avenues have been explored to gain control of uveitis flares in these patients (Haibel et al, 2013).

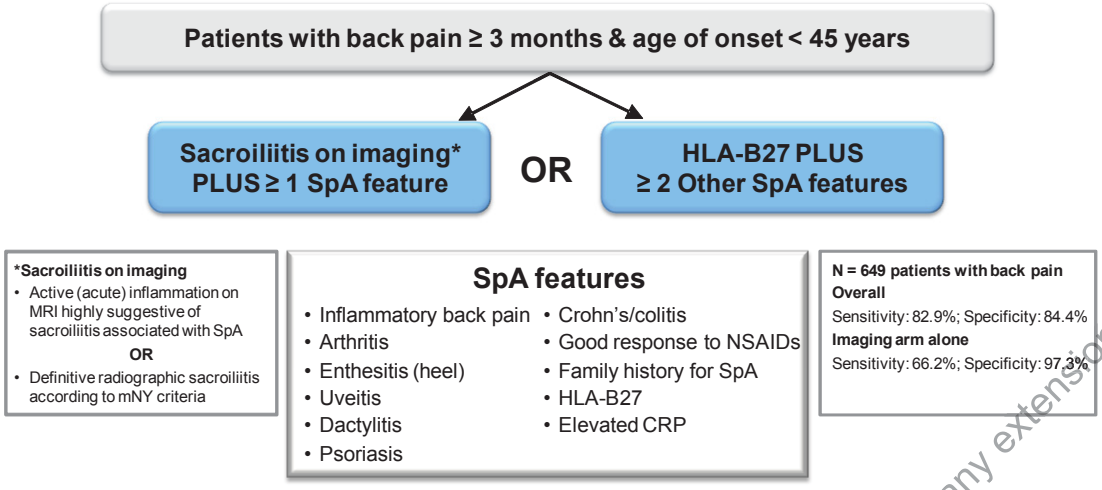
Analyses of uveitis flares from multiple randomized controlled trials (RCTs), in which patients received anti-tumor necrosis factor (TNF) therapy for the treatment of AS, have demonstrated a significant reduction in the incidence of acute AU flares in AS patients compared to that demonstrated in those patients who received placebo (Huscher et al, 2006). Furthermore, data from a large open-label non-controlled study demonstrated a significant reduction in the rate of AU flares following adalimumab (ADA) treatment of AS patients (Kobelt et al, 2004). A UCB study by Van Denderen et al, 2014, a pooled data analysis (Huscher et al, 2006), and a recent review (Rosenbaum et al, 2014) have suggested that the monoclonal antibodies ADA and infliximab (IFX) are equally effective in reducing AU flares, and are superior to etanercept (ETN) in this regard. However, at present, there are no RCT data available demonstrating the efficacy of anti-TNF in the reduction of uveitis flares in an axSpA population.

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 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, 1984), 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, 2009b; Rudwaleit et al, 2009c). 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 magnetic resonance imaging [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 SIJ inflammation or radiographic evidence of sacroiliitis meeting the 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 (classification criteria); MRI=magnetic resonance imaging; NSAID=nonsteroidal anti-inflammatory drug; SpA=spondyloarthritis.
Source: Rudwaleit et al, 2009c

2.4 Current management of axial spondyloarthritis and uveitis

Based on the current treatment recommendations developed by ASAS and the European League Against Rheumatism for axSpA, first-line therapy consists of NSAIDs and nonpharmacologic treatment, such as patient education and regular exercise/physiotherapy (Braun et al, 2011). Nonsteroidal anti-inflammatory drugs usually have a rapid initial effect for the symptoms pain and stiffness of axSpA (Poddubnyy et al, 2012; Poddubnyy et al, 2013), but many patients lose symptomatic response and structural damage often progresses despite their use. Conventional DMARDs (eg, MTX and SSZ) have limited efficacy in axial disease but may benefit patients with peripheral joint disease (Braun et al, 2006; Haibel et al, 2005; Haibel et al 2007). 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, ADA, ETN, IFX, and golimumab [GOL]) are currently the only effective and approved treatment options.

Uveitis can be caused by infectious and noninfectious etiologies. The precise diagnosis is crucially important to establish the most accurate therapy.

For most noninfectious uveitis, the control of inflammation is the key to treatment success. The normal option is a stepladder approach and the treatment includes local corticosteroids, systemic corticosteroids, and systemic immune modulators, often sequentially starting with topical therapy. Noninfectious uveitis is often associated with other systemic conditions, such as HLA-B27-related spondyloarthropathies, inflammatory bowel disease, JIA, Behcet's Disease, and sarcoidosis. The treatment of systemic symptoms may also improve the ocular inflammation.

Systemic immunomodulatory medications used for ocular inflammatory conditions include conventional immunosuppressive agents and biologic response modifiers. The agents include antimetabolites, inhibitors of T-cell signaling, and alkylating agents.

Biologic therapy can be an alternative in patients with inadequate response to or intolerance of conventional immunotherapy. Biologicals were developed and approved to treat systemic inflammatory diseases or to prevent organ transplantation rejection. Several biologicals are approved for the treatment of axSpA, however none have been approved in the USA or the EU specifically for the treatment of uveitis but have been used off-label to treat uveitis or ocular inflammation.

2.5 Rationale

Noninfectious AU is characterized by a genetic disposition expressed by positive HLA-B27. Spondyloarthritis (SpA) represents the most frequent extra-ocular manifestation observed in patients with HLA-B27 associated AU. The prevalence of SpA in subjects with HLA-B27 positive AU reportedly ranges from 13% to 58.3% (Monnet et al, 2004; Rosenbaum, 1989).

The prevalence of AU is variable between the different types of SpA. Considering the 3 most frequent SpA (AS, psoriatic arthritis [PsA], and IBD-associated SpA), it is generally understood that in patients with AS, there is a greater frequency of AU in patients with AS compared to the other 2 disorders. Anterior uveitis at onset or complicating the disease course has been reported in 33% of patients with AS, while the reported percentages are lower in PsA and IBD-associated SpA (Zeboulon et al, 2008). Therefore, AU represents the most frequent extra-articular manifestation and is often also the starting point to recognizing the spinal involvement and AS.

The extra-articular manifestations in AS are seen in more than one-third of the AU patients and, within this set of manifestations, uveitis represents the largest group with 51% of the extra-articular manifestations. This means that 20% of the axSpA patients are confronted with uveitis at some point during their lifetime.

While uveitis flares are usually infrequent and are managed with topical therapies, an important subset has frequent treatment refractory flares.

A significant amount of data exists for ADA and IFX for the treatment of uveitis and the prevention of flares, but neither agent is approved (ADA in Phase 3) at the moment for this indication. Although CZP belongs to the same group of agents, less data are available.

Certolizumab pegol, a PEGylated Fragment crystallizable-free anti-TNF, has been shown to improve spinal and extra-articular manifestations, such as enthesitis and peripheral arthritis, in patients with axSpA (including both AS and nr-axSpA patients) (Landewé et al, 2014).

Emerging data from a retrospective case series indicate a treatment effect of CZP in active refractory uveitis (Myasoedova et al, 2010) and justifies further research. Further data are required to determine the effectiveness of CZP in reducing the incidence of uveitis flares in axSpA patients, an important facet of disease symptomatology (Olivieri et al, 2013).

AS0007 will investigate the effect of CZP treatment on the frequency of AU flares in subjects with axSpA.

3 STUDY OBJECTIVE(S)

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

A flare is defined as being a new episode of AU that, based on the judgment of an ophthalmologist, requires specific treatment. A flare is considered a new episode if a gap of at least 3 months occurs between 2 flares.

3.1 Primary objective

The primary objective of the study will be to demonstrate the effect of CZP treatment on the reduction of AU flares in subjects with active axSpA and a documented history of AU.

3.2 Secondary objectives

The secondary objectives of the study will be to assess the effect of CZP treatment on:

- The reduction of AU flares in subjects with active axSpA having at least 1 documented history of AU within 12 months prior to Baseline
- AxSpA disease activity

3.3 Other objectives

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

- Physical function
- Signs and symptoms of axSpA
  - Morning stiffness
  - Fatigue
  - Extra-articular manifestations of axSpA
- Duration and severity of AU flares

3.4 Safety objective

The safety objectives of the study will be to evaluate the safety and tolerability of CZP therapy.

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variable

The primary efficacy variable will be the count of distinct episodes of AU flares during the Treatment Period.

4.1.2 Secondary efficacy variables

The following secondary efficacy variables will be assessed at Week 48 and Week 96:

- Number of AU flares per 100 patient-years in subjects with active axSpA and a history of AU

- Number of AU flares per 100 patient-years in subjects with active axSpA and at least 1 AU episode within 12 months prior Baseline
- Change from Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS)
- Change from Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Assessment of ASAS 20, 40, 5/6, and partial remission (PR) response rates
- Change from Baseline in tender and swollen joint count (44 joint count); Physician's Global Assessment of Disease Activity (PhGADA).
- Change from Baseline in the respective components of the ASAS response criteria, assessed by:
  - Patient's Global Assessment of Disease Activity (PtGADA)
  - Pain assessment (total spinal pain Numerical Rating Scale [NRS])
  - Function (represented by Bath Ankylosing Spondylitis Functional Index [BASFI])
  - Inflammation (the mean of the BASDAI questions 5 and 6 concerning [redacted])

4.1.3 Other efficacy variables

The following other efficacy variables will be assessed at the timepoints indicated in Table 5-1:

- Duration of AU flares
- Severity of AU flares
- Change from Baseline in ASDAS
- Change from Baseline in BASDAI
- ASAS 20, 40, 5/6, and PR response rates
- Change from Baseline in tender and swollen joint count (44 joint count), PhGADA.
- Change from Baseline in the respective components of the ASAS criteria, assessed by:
  - PtGADA
  - Pain assessment (total spinal pain NRS)
  - Function (represented by BASFI)
  - Inflammation (the mean of the BASDAI questions 5 and 6 concerning [redacted])
- Change from Baseline in ASDAS disease activity (clinical improvement [CI], major improvement [MI], inactive disease [ID], clinically important improvement [CII]), and BASFI) (including Weeks 48 and 96)
- Change from Baseline in [redacted] (NRS) (from BASDAI) (including Weeks 48 and 96)
- Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) (including Weeks 48 and 96)

- Change from Baseline in ASAS Health Index (HI) questionnaire (including Weeks 48 and 96)
- Change from Baseline in Short-Form 36-Item Health Survey (SF-36) (including Weeks 48 and 96)
- Number of IBD exacerbations
- Number of psoriasis exacerbations (in subjects with concurrent psoriasis)

4.2 Safety variables

4.2.1 Secondary safety variable

The secondary safety variable to be assessed is treatment-emergent adverse events (TEAEs).

4.2.2 Other safety variables

The following other safety variables to be assessed are:

- Blood pressure
- Physical examination
- Clinical laboratory values (hematology, biochemistry, and urinalysis)

5 STUDY DESIGN

5.1 Study description

AS0007 is a multicenter, open-label, Phase 4 study to evaluate the effect of CZP on the incidence of AU flares per year in subjects with both active axSpA and a history of AU by comparing the historical AU flare rate that occurred prior to CZP treatment with the AU flare rate occurring while under CZP treatment.

The study duration from the start of treatment will be 96 weeks from Baseline onwards, and a FU Visit will be performed at Week 104, 10 weeks after the final dose. A schedule of study assessments is provided in Table 5-1.

The study includes 3 periods as follows:

- **Period 1** (Screening Period): 1 to 5 weeks before Baseline

Subjects will be informed about the study and sign the ICF. Eligibility will be evaluated and assessments will be performed as listed in Table 5-1. The Screening Period should be kept as short as possible but can be extended to 5 weeks if certain medications need to be washed out or to allow to obtain information from the subject's ophthalmologist. For subjects who start a prophylactic treatment for LTBI, the Screening Period can be extended up to 12 weeks (see Section 10.6.4.1).

- **Period 2** (Treatment Period): Week 0 to Week 96

Eligible subjects will receive a dose of CZP 400mg sc administered at Baseline, Week 2, and Week 4 followed by CZP 200mg sc Q2W (starting at Week 6 until Week 94).

All subjects will be trained at the beginning of the study on self-administration before the subjects start with self-administration (relative or caregiver may also perform the injections). The

injection schedule will provide the sequence of self-administration and site visits including injection at the site.

- **Period 3** (FU Period): 10 weeks from the final dose of study medication received.

All subjects will have a FU Visit at Week 104 or earlier in case of an early WD, 10 weeks after the final CZP administration received within the study.

A Week 48 analysis will be performed after all subjects have either completed the Week 48 Visit or have prematurely withdrawn prior to the Week 48 Visit. The final analysis will be conducted at the end of the study after all study data is locked.

5.1.1 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 (see Section 10.6.4.1 for details on an extended Screening Period of 12 weeks)
- A Treatment Period of 96 weeks
- A FU Visit at Week 104

The end of the study is defined as the date of the last study FU Visit.

5.1.2 Planned number of subjects and sites

Approximately 130 subjects will be screened in order to enroll 86 subjects into the study.

The estimated recruitment period will be approximately 12 months. This takes into account an estimate of a 35% screen failure rate between Screening and Baseline. Prematurely discontinued randomized subjects will not be replaced.

Subjects are planned for enrollment at approximately 20 to 30 sites.

5.1.3 Anticipated regions and countries

The study will be conducted in Europe.

5.2 Schedule of study assessments

The Schedule of Assessments is shown in Table 5-1. A study schematic is presented in Figure 5-2.

Table 5-1: Schedule of assessments

Study Period	Period 1 (Screening)	Period 2 (Open-Label)												Period 3 FU
Week (W) Protocol Activity	**-5 to -1[a]**	**0 BL**	**2**	**4**	**12**	**24**	**32**	**36**	**48**	**60**	**72**	**84**	**96/ WD**	**104**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Written informed consent[b]	X													
Assessments for inclusion/exclusion criteria	X	X												
Demographic data	X													
Medical history (including axSpA history, and tobacco use) and concomitant diseases	X													
Prior and concomitant medication[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Uveitis history	X													
Uveitis flare evaluation		X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[e]	X	X	X	X	X	X		X	X	X	X	X	X	X
Extra-articular assessments[f]	X	X			X	X		X	X	X	X	X	X	

Study Period	Period 1 (Screening)	Period 2 (Open-Label)												Period 3 FU
Week (W) Protocol Activity	**-5 to -1[a]**	**0 BL**	**2**	**4**	**12**	**24**	**32**	**36**	**48**	**60**	**72**	**84**	**96/ WD**	**104**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Hematology/ urinalysis/ biochemistry/	X[g]	X	X	X	X	X		X	X	X	X	X	X	
CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy testing[h]	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	
MRI (nr-axSpA subjects only)[k]	X													
X-ray (AS subjects only)[l]	X													
BASDAI	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	
ASQoL		X	X	X	X	X		X	X	X	X	X	X	
ASAS HI questionnaire		X	X	X	X	X		X	X	X	X	X	X	
SF-36		X	X	X	X	X		X	X	X	X	X	X	
PtGADA		X	X	X	X	X	X	X	X	X	X	X	X	

Study Period	Period 1 (Screening)	Period 2 (Open-Label)												Period 3 FU
Week (W) Protocol Activity	**-5 to -1[a]**	**0 BL**	**2**	**4**	**12**	**24**	**32**	**36**	**48**	**60**	**72**	**84**	**96/ WD**	**104**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Total and nocturnal spinal pain		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	
PhGADA		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
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug sc injections[m]		X	X	X	X	X	X	X	X	X	X	X		
Schedule appointment for next visit	X	X	X	X	X	X	X	X	X	X	X	X	X	

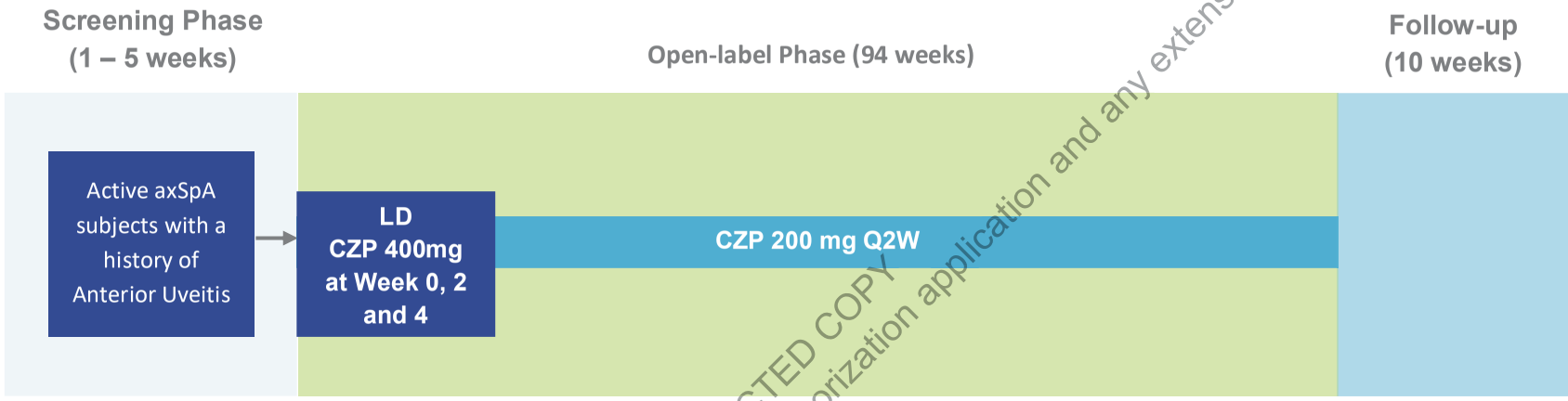
AE=adverse event; AS=ankylosing spondylitis; ASAS=Assessment of SpondyloArthritis international Society; ASQoL=Ankylosing Spondylitis Quality of Life; axSpA= axial spondyloarthritis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BL=Baseline; CRP=C−reactive protein; FU=Follow-up; HI=Health Index; HLA-B27= human leukocyte antigen B27; IBD=inflammatory bowel disease; IWRS=Interactive Web Response System; LTBI=latent tuberculosis infection; mNY=modified New York (classification criteria); MRI=magnetic resonance imaging; nr-axSpA=nonradiographic axSpA; PhGADA=Physician's Global Assessment of Disease Activity; PtGADA=Patient's Global Assessment of Disease Activity; Q2W=every 2 weeks (every other week); sc=subcutaneous(ly); SF-36=Short-Form 36-Item Health Survey; SIJ=sacroiliac joint; TB=tuberculosis; WD=Withdrawal

Study Period	Period 1 (Screening)	Period 2 (Open-Label)												Period 3 FU
Week (W) Protocol Activity	-5 to -1[a]	0 BL	2	4	12	24	32	36	48	60	72	84	96/ WD	104
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14

[a] For subjects with LTBI who initiate a prophylactic treatment and need to have 8 weeks of prophylactic treatment prior to randomization, the Screening Period can be extended to 12 weeks. For other subjects, the Screening Period should be kept as short as possible, but can be up to 5 weeks if certain medications need to be washed out or to allow to obtain information from the subjects' ophthalmologist.
[b] Informed consent: prior to any study activities, subjects will be asked to read and sign the informed consent form.
[c] Past medications will recorded at Screening. Concomitant medications will be recorded at all other visits.
[d] Pulse rate, systolic and diastolic blood pressures, and temperature are to be measured at Screening and Baseline, thereafter systolic and diastolic blood pressures are to be measured.
[e] Weight is to be measured at Screening, Baseline, Week 48, and at completion at Week 96/WD Visit. Height will be measured at the Baseline Visit only.
[f] Extra-articular assessments includes the number of IBD exacerbations and number of psoriasis exacerbations (in subjects with concurrent psoriasis)
[g] Testing to rule out hepatitis B core antibody, hepatitis B surface antigen, hepatitis B surface antibody, antibodies to hepatitis C, and antibodies to human immunodeficiency virus at Screening only. Testing for HLA-B27 at Screening, only if not performed before.
[h] Pregnancy testing for women of childbearing potential will be serum testing at the Screening Visit and urine dipstick testing at Baseline and Week 96/WD Visit and the FU Visit (10 weeks after the final dose of study drug).
[i] Chest x-ray used for screening must have been done within 3 months prior to the 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). If no chest x-ray is available within the 3 months prior to the Screening Visit, the x-ray can be done during the Screening Period.
[j] QuantiFERON TB GOLD test. The TB tests will be repeated at Week 48 and 96 (or at WD Visit if medically indicated) for subjects with previously negative TB test result.
[k] For subjects with nr-axSpA, an MRI of the SIJs is to be performed during the Screening Period. An MRI performed ≤3 months prior to the Baseline Visit may be used as the Baseline. An MRI assessment is not needed for patients with AS.
[l] AS subjects must have evidence of sacroiliitis on x-ray taken prior to Baseline meeting the mNY classification criteria according to the Investigator. If not available, this x-ray is to be taken during the Screening Period. If an x-ray was performed prior to the Screening Visit and the mNY classification criteria were met, the x-ray is not to be repeated.
[m] Onsite study drug administration will occur after all other visit assessments are completed and laboratory samples are drawn. Study drug injections will occur at home Q2W on Weeks 6, 8, and 10, 14 to 22, 26 to 30, 34, 38 to 46, 50 to 58, 62 to 70, 74 to 82, and 86 to 94. At all visits, an even number of syringes (2 per box) will be assigned (eg, at Week 4 syringes will be assigned for Weeks 6, 8, and 10; 1 syringe will be returned by the subject at Week 12).

5.3 Schematic diagram

Figure 5-2: Schematic diagram



axSpA=axial spondyloarthritis; CZP=certolizumab pegol; LD=loading dose; Q2W=every 2 weeks

5.4 Rationale for study design and selection of dose

The aim of the study is to evaluate the flare rate of AU before the start of CZP treatment compared to that of a period with CZP treatment. Since the occurrence of flare is both subject and disease specific, each subject should act as his/her own control. Because an untreated uveitis flare can cause severe eye complication, it was deemed necessary to treat all subjects with an active drug.

Therefore, 1 treatment arm with 1 set of subjects is deemed the right approach to allow for the comparison of the history of flare occurrence with the flare occurrence on a biological treatment in the same subjects. The dose of CZP used in this study is the same as per label to treat axSpA subjects, which has been shown to be [redacted] and effective for reducing the main axSpA symptoms.

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.
2. Subject 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 at the Screening Visit.
4. Female subjects must be either postmenopausal for at least 1 year, surgically incapable of childbearing, or effectively practicing an acceptable method of contraception (including oral/parenteral/implantable hormonal contraceptives, intrauterine device or barrier and spermicide or contraception methods that are considered as at least as safe for contraception). Abstinence only is not an acceptable method. Subjects must agree to use adequate contraception during the study and for at least 5 months (in accordance with the Summary of Product Characteristics [SPC]) after the last dose of study treatment. Male subjects must agree to ensure that they or their female partner(s) use adequate contraception during the study and for at least 5 months (in accordance with the SPC), 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 criteria (according to Appendix 16.2).

6a. Subjects must have active disease at Screening as defined by

- BASDAI score ≥ 4
- Spinal pain ≥ 4 on a 0 to 10 NRS (from BASDAI item 2)
- Nr-axSpA subjects must either have CRP > upper limit of normal (ULN) and/or current evidence of sacroiliitis on MRI (no confirmation by central reading) as defined by ASAS criteria

- AS subjects must have evidence of sacroiliitis on x-ray meeting the mNY classification criteria according to the Investigator

7. Subjects must have a documented history of AU diagnosed by an ophthalmologist and have at least 2 AU flares in the past, of which at least 1 AU flare was in the last 12 months prior to Baseline.
8. Subjects must be HLA-B27 positive (if known prior to Screening, no additional testing is to be performed; if unknown, testing is to be performed at Screening and checked at Baseline).
9. Subjects must have been intolerant to or had an inadequate response 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. The subject has previously participated in this study or has previously received CZP treatment in or outside of another clinical study. However rescreening is possible if prophylactic treatment for LTBI was to be given but the Screening Period exceeded the 12 weeks.
2. The subject has participated in another study of an investigational medicinal product (IMP) (or a medical device) within the previous 3 months or is currently participating in another study of an IMP (or a medical device).
3. The subject has a history of chronic alcohol or drug abuse.
4. The 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. The subject has a known hypersensitivity to any components of CZP or a history of an adverse reaction to polyethylene glycol (PEG).

Axial SpA-disease-related exclusions

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

Ophthalmic exclusion criteria

8. Any history of uveitis (eg, posterior, panuveitis) except for AU associated with axSpA.

9a. Any condition or complicating factor that may interfere with the AU assessment, for example:

   a. History of cataract surgery within 6 months prior to Baseline

b. Corneal or lens opacity

c. Proliferative or severe nonproliferative diabetic retinopathy or clinically significant macular edema due to diabetic retinopathy

d. Neovascular/wet age-related macular degeneration

e. History of scleritis

f. History of intraocular surgery, with the exception of phacoemulsification

10. Subject has Retisert® or Iluvien® (glucocorticosteroid implant) within 3 years prior to the Baseline Visit or has had complications related to the device. Subject has had Retisert or Iluvien (glucocorticosteroid implant) removed within 90 days prior to the Baseline Visit or has had complications related to removal of the device.
11. Subject has received intraocular or periocular corticosteroids within 90 days prior to the Baseline visit.
12. Subject has received Ozurdex® (dexamethasone implant) within 6 months prior to the Baseline Visit.
13. Subject on cyclophosphamide within 30 days prior to the Baseline Visit.
14. Subject has received intravitreal MTX within 90 days prior to the Baseline Visit.
15. Subject has received intravitreal anti-vascular endothelial growth factor (VEGF) therapy:

    a. Within 45 days of the Baseline visit for Lucentis® (ranibizumab) or Avastin® (bevacizumab)

    or

    b. Within 60 days of the Baseline visit for anti-VEGF Trap Zaltrap® (aflibercept)

Prior medications exclusions

16a. Subjects must not have used the following medications in the manner as detailed by the exclusion criteria in Table 6–1.

Table 6–1: Concomitant Medications (Prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria
Analgesics (including, but not limited to acetaminophen, paracetamol, NSAIDs, opiates or combinations thereof)	Any dose	PRN doses of an analgesic should not be used within 24 hours of Baseline or any other Study Visit. Stable doses of analgesics (including narcotics) are to be maintained throughout the study.
NSAIDs/cyclooxygenase 2 (COX 2) inhibitors	Any dose regimen	PRN doses of an NSAID should not be used within 24 hours of Baseline or any other Study Visit. Any change in stable dose in the 14 days prior to the Baseline Visit is exclusionary. Stable doses of NSAIDs are to be maintained throughout the study.
Oral corticosteroids (for AU only)	Maximum allowed ≤10mg daily total prednisone equivalent[a]	Any change in stable dose in the 28 days prior to the Baseline Visit is exclusionary. Oral corticosteroid tapers of less than 14 days used to treat other indications (asthma exacerbation, contact dermatitis, etc.) during the study are allowed as long the maximum daily dose is ≤20mg
Intramuscular (im) corticosteroids	Any dose	Use in the 28 days prior to the Baseline Visit is exclusionary.
Intra-articular (ia) corticosteroids	Any dose	Use in the 28 days prior to the Baseline Visit is exclusionary.
Intravenous (iv) corticosteroids	Any dose	Any exposure during study is not allowed.
Intra-articular hyaluronic acid	Any dose	Use in the 28 days prior to the Baseline Visit is exclusionary.
Disease-modifying antirheumatic drugs (DMARDs): sulfasalazine (SSZ) and/or hydroxychloroquine (HCQ) and/or methotrexate (MTX) and/or leflunomide (LFN) and/or azathioprine (AZA)	Maximum allowed: SSZ ≤3g daily HCQ ≤400mg daily MTX ≤25mg weekly AZA ≤150mg daily LFN ≤20mg daily	Use initiated in and/or any change in the dose regimen in the 28 days prior to the Baseline Visit is exclusionary. DMARDs dose should be kept stable throughout the study except for reasons of intolerance, where the DMARD dose may be decreased.

Table 6–1: Concomitant Medications (Prior to Baseline and Study Visits)

Drug class	Dose	Exclusion criteria
DMARDs: cyclosporine, cyclophosphamide, mycophenolic acid, apremilast	Any dose	Use within 28 days prior to the Baseline Visit is exclusionary. Must not be started during the study.
Biologicals: infliximab (IFX) adalimumab (ADA) etanercept (ETN) golimumab (GOL)	Any dose	For IFX, ADA, and GOL, any use within the 3 months prior to the Baseline Visit. For ETN, use within the 28 days prior to the Baseline Visit. Only 1 previous biological is allowed.
Other biologicals eg, abatacept (ABA) anti CD20 tocilizumab ustekinumab secukinumab certolizumab pegol (CZP)	Any dose	Any exposure history. Must not be started during the study.

AU= anterior uveitis; DMARD=disease modifying antirheumatic drug; NSAID=nonsteroidal anti-inflammatory drug; PRN=as needed; STJ= swollen and tender joint

[a] A table of corticosteroid equivalent doses is provided in Appendix16.3, Table 16–1.

Previous clinical studies and previous biological therapy exclusions

17. Subjects must not have received any nonbiological therapy for axSpA not listed in Table 6–1 within or outside of a clinical study in the 3 months or within 5 half lives prior to the Baseline Visit (whichever is longer).
18. Subjects must not have received any experimental biological agents (defined as those agents unlicensed for use in axSpA in the EU or the USA).
19. Subjects must not have received previous treatment with a PEGylated compound that resulted in a severe hypersensitivity reaction or an anaphylactic reaction.
20. Subjects must not have been exposed to more than one TNF antagonist prior to the baseline visit and may not be a primary failure to any TNF antagonist therapy (defined as no response within the first 12 weeks of the TNF antagonist treatment).

Medical history exclusions

21. Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the study or within 5 months (or longer, if required by local regulation) following the final dose of the investigational product.

22. Subjects with a history of chronic or recurrent infections, excluding uveitis (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).
23. Subjects with a history of herpes zoster infection within 6 months prior to the Baseline Visit.
24. Subjects with known tuberculosis (TB) infection, at high risk of acquiring TB infection, or LTBI.
    a. Known TB infection whether present or past is defined as:
    – Active TB infection or clinical signs and symptoms suspicious for TB (pulmonary or extrapulmonary)
    – 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) is defined as:
    – The absence of signs, symptoms (ie, evidence of organ-specific involvement), or physical findings suggestive of TB infection with a positive interferon-gamma release assay (IGRA; 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 is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be randomized to study medication without further evaluation, treatment, and discussion with Study Physician, if LTBI 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 (Centers for disease control diagnosis of LTBI, http://www.cdc.gov/TB/topic/testing/default.htm)

      Detailed information on TB definition, clinical signs, diagnosis, documentation, and treatment will be available in this protocol.
25. Subjects with current acute or chronic viral hepatitis B or C or with human immunodeficiency virus (HIV) infection.

26. Subjects with current or a history of active infection with *Histoplasma*, *Coccidiodes*, *Paracoccidioides*, *Pneumocystis*, nontuberculous mycobacteria, *Blastomyces*, or *Aspergillus.*
27. Subjects with a history of an infected joint prosthesis at any time.
28. 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).
29. 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).
30. Subjects with a history of a lymphoproliferative disorder, including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.
31. 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).
32. Subjects with Class III or IV congestive heart failure as per the New York Heart Association 1964 criteria.
33. Subjects with a history of, or suspected, demyelinating disease of the central nervous system (eg, multiple sclerosis or optic neuritis).
34. 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.
35. Subjects with a history of or a current, as determined by the Investigator, severe, progressive, and/or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, or neurological disease.
36. Subjects with significant laboratory abnormalities at Screening including but not limited to:
    - Liver function tests >2.0 x ULN
    - Estimated Glomerular Filtration Rate<60 mL/min/1.73^2 as measured by Chronic Kidney Disease Epidemiology Collaboration (Levey et al, 2009)
    - White blood cell (WBC) count <3.0x10^9/L.
37. Subjects with any other condition which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study

6.3 Withdrawal criteria

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

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

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 regulatory agency requests withdrawal of the subject.
7. The Sponsor requests withdrawal of the subject for safety reasons.
8. 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 LTBI, no prophylactic treatment was initiated (see Section 10.6.4).
9. Subject who prematurely discontinues treatment for latent TB or, in the opinion of the Investigator or Sponsor, is noncompliant with anti-TB therapy, must be withdrawn.

Once withdrawn from study treatment, subjects must return for a Withdrawal Visit and perform all assessments as defined for the W96/WD Visit in Table 5-1, and complete a final FU Visit, 10 weeks after the last dose of study medication is administered.

Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered 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 (CRF) 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.

7 STUDY TREATMENT(S)

7.1 Description of investigational medicinal product(s)

For the purpose of the protocol IMP refers to CZP. 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 site will be adapted to the recruitment capacity of that site and to the expiry date of the IMP and will be managed by the interactive web response system (IWRS).

Certolizumab pegol is an engineered humanized monoclonal antibody Fab´ fragment with specificity for human TNFα, manufactured in E. coli. The antibody fragment is subsequently purified and conjugated with high molecular weight PEG (40kDa).

Certolizumab pegol will be supplied as a sterile, clear, colorless to-slightly yellow liquid solution with a pH of approximately 4.7 in 1mL single-use glass prefilled syringe with a thin-walled needle for sc injection. Each syringe will contain 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.

7.2 Treatment(s) to be administered

The IMPs will be administered as sc injections into either the lateral abdominal wall or the upper outer thigh. Each injection should be administered at a separate injection site, and rotation between the injection sites should be observed. Before injection, the PFS should be brought to room temperature. Certolizumab pegol will be administered as 400mg at Baseline and Weeks 2 and 4 followed by 200mg Q2W (starting at Week 6 until Week 94). Subjects will be trained by the qualified, designated, site personnel and be provided with written instructions on the correct injection technique. Once the subject is trained at the start of the study the subject will have the opportunity to self-inject IMP. Site personnel must investigate whether the subjects have adequate storage conditions at home and are willing and able to perform the injection of IMP. Subjects who opt for self-administration may also request that a designated caregiver/family member administers the IMP. This person must attend all protocol-required training and be tested and judged as capable of administering the study medication to the subject.

7.3 Packaging

Certolizumab pegol is packaged and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations. It is suitably packaged in such a way as to protect the IMP from deterioration during transport and storage.

7.4 Labeling

Certolizumab pegol packaging will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

7.5.1 Storage at the site

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. The IMP stored by the Investigator should be kept in a secured area with limited access.

The IMP containers should be under conditions as detailed in the IMP manual. In case an out-of-range temperature is noted, it must be immediately communicated within the IWRS and UCB as described in the IMP manual before further use of the IMP.

Appropriate storage conditions (storage of CZP is to be done at 2 to-8ºC) must be ensured and completion of a temperature log in accordance with local requirements must be done on

a regular basis (eg, once a week), but at least once per working day showing minimum and maximum temperatures reached over the time interval. In case of an out of range temperature, based on discussion with a UCB Quality Assurance representative, the Drug Supply Coordinator will then provide the site with instructions regarding use of the IMP and adjust the status of the IMP as needed in the IWRS.

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

7.5.2 Storage at the subject's home

The Investigator (or designee) will instruct the subject how to handle the IMP during transport and how to store the IMP as per the label. Specific emphasis on the transport from site to home is required and instructions on the use of cold bags for CZP syringes must be followed. The subject is instructed to put the syringes as quickly as possible into his/her refrigerator.

In the case of a malfunctioning refrigerator or damaged or lost syringes, the subject must inform the site immediately and new syringes will be provided.

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 return or destruction.

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.

7.7 Procedures for monitoring subject compliance

At each on-site visit after IMP is dispensed, subjects must return all used and unused IMP to the site.

Drug accountability must be recorded on the drug accountability form.

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)

7.8.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study for uveitis:

- 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 (see Table 6–1).
  - 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.

The following concomitant medications are permitted during the study for axSpA:

- NSAIDs/cyclooxygenase 2 (COX-2) inhibitors
  - Stable doses of analgesics established at Baseline (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 (see Table 6–1).
  - 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) administration of corticosteroids is 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) 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.
- Disease-modifying antirheumatic drugs (DMARDs) (only SSZ and/or hydroxychloroquine [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 DMARDs 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, ia, or iv) 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 DMARDs (cyclosporine, cyclophosphamide, mycophenolic acid, apremilast). Biologicals (TNF antagonists: IFX, ADA, ETN, GOL; abatacept [ABA]; CZP; Rituximab or other anticluster of differentiation 20 [anti-CD20] antibodies; tocilizumab; ustekimumab; tofacitinib; or any other biological response modifiers that 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 electronic Case Report Form (eCRF).

7.8.3 Rescue medication

A rescue medication is any medication other than prohibited medication that is used to treat axSpA or uveitis. The use of rescue medication is allowed during Screening through Week 96/WD Visit, except under the conditions noted in Section 7.8.2.

7.9 Blinding

This will be an open-label study; therefore, blinding is not applicable.

7.10 Enrollment into treatment and numbering of subjects

An IWRS will be used for assigning CZP treatment to eligible subjects. The IWRS will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

To enroll a subject into the study (Visit 1), the Investigator or designee will contact the IWRS 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 communications between the Investigator or designee and the IWRS regarding a particular subject. Subject numbers and kit numbers will be tracked via the IWRS.

To enroll a subject into the Treatment Phase, the Investigator or designee will contact the IWRS and provide brief details about the subject to be enrolled. The IWRS will automatically allocate kit numbers to the subject based on the subject number during the course of the study.

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 FU Period of 10 weeks after the last dose of the study drug. For Week 2 to Week 96 the visit window is ±3 days from the actual date in Weeks from the initial administration of IMP (Week 0). For the FU Visit a window of 1-2 weeks is acceptable.

8.1 Visit 1 (Week -5 to -1) Screening

Prior to any study activities, subjects will be asked to read and sign an informed consent form (ICF) for participation in the study. All ICFs will have been approved by an IEC/IRB and will 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:

- Confirm informed consent
- Review inclusion/exclusion criteria
- Demographic data (includes date of birth, gender, race/ethnicity)
- Washout of excluded medications (3 months for TNFs)
- Significant past medical and procedure history (including tobacco use) and concomitant disease (including axSpA history)
- Prior and concomitant medication
- Review of the uveitis history containing all documented UA
- Vital signs (pulse rate, systolic and diastolic blood pressures, and temperature)
- Physical examination (including weight) and extra-articular assessment (including the number of IBD exacerbations and number of psoriasis exacerbations [in subjects with concurrent psoriasis])

- Hematology, biochemistry, and urinalysis for clinical laboratory values
- Hepatitis-associated disease markers assessment:
  - Hepatitis B core antibody (HBc-Ab)
  - Hepatitis B surface antigen (HBs-Ag)
  - Hepatitis B surface antibody (HBs-Ab)
  - Hepatitis C virus antibody (HCV-Ab)
- Testing of antibodies to HIV
- Testing for HLA-B27 if unknown at Screening Visit
- CRP testing
- Serum pregnancy testing for women of childbearing potential
- TB evaluation
  - Screening chest x-ray must have occurred within 3 months prior to 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).
  - TB: IGRA test (QuantiFERON TB GOLD test).
  - TB evaluation questionnaire (includes evaluation of signs and symptoms of active TB and risk factors for exposure to TB)
- Chest x-ray used for screening must have been done within 3 months prior to the 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). If no chest x-ray is available within the 3 months prior to the Screening Visit, the x-ray can be done during the Screening Period.
- For subjects with nr-axSpA, an MRI of the SIJs is to be performed during the Screening Period. An MRI performed ≤3 months prior to the Baseline Visit may be used as the Baseline. An MRI assessment is not needed for patients with AS.
- AS subjects must have evidence of sacroiliitis on x-ray taken prior to Baseline meeting the mNY classification criteria according to the Investigator. If not available, this x-ray is to be taken during the Screening Period. If an x-ray was performed prior to the Screening Visit and the mNY classification criteria were met, the x-ray is not to be repeated.
- BASDAI
- Contact the IWRS to indicate the subject has been screened
- Schedule appointment for next visit

The Screening chest x-ray should be read by an experienced TB imaging specialist, radiologist, pulmonologist or infectious disease specialist, who is specifically requested to look for signs of active TB or signs of past/inactive TB infection and must exclude evidence of TB. For subjects with LTBI who initiate a prophylactic treatment and need to have

8 weeks of prophylactic treatment prior to randomization, the Screening Period can be extended to 12 weeks. For other subjects, the Screening Period should be kept as short as possible, but can be up to 5 weeks if certain medications need to be washed out or to allow to obtain information from the subjects' ophthalmologist.

8.2 Visit 2 (Week 0) Baseline Visit

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

- Review of inclusion/exclusion criteria
- Evaluation of uveitis flares that occurred since last visit
- Prior and concomitant medications
- Vital signs (pulse rate, systolic and diastolic blood pressure, and temperature)
- Physical examination and extra-articular assessment
  - Height
  - Weight
  - Number of IBD exacerbations
  - Number of psoriasis exacerbations (in subjects with concurrent psoriasis)
- Blood samples will be collected for
  - Hematology analyses
  - Biochemistry analyses
  - CRP testing
- Urine will be collected for
  - Urinalysis
  - Urine pregnancy test for women of childbearing potential
- TB questionnaire
- Patient reported outcomes:
  - BASDAI
  - BASFI
  - ASQoL
  - ASAS HI questionnaire
  - SF-36
  - Total and nocturnal spinal pain
  - PtGADA

- PhGADA
- Swollen and tender joint counts
- AEs
- Contact IWRS to enroll subject and to obtain kit numbers
- Study drug administration on-site (after all other visit assessments are completed and laboratory samples are drawn)
- Schedule appointment for next visit

8.3 Visit 3 and 4 (Week 2 and 4)

Assessments at these visits will include:

- Evaluation of uveitis flares that occurred since last visit
- Concomitant medications
- Vital signs (systolic and diastolic blood pressures)
- Physical examination
- Blood samples will be collected for
  - Hematology analyses
  - Biochemistry analyses
  - CRP testing
- Urine will be collected for urinalysis
- Patient reported outcomes:
  - BASDAI
  - BASFI
  - ASQoL
  - ASAS HI questionnaire
  - SF-36
  - Total and nocturnal spinal pain
  - PtGADA
- PhGADA
- Swollen and tender joint counts
- AEs
- Contact IWRS to obtain kit numbers

- Study drug administration on-site. At Week 4, syringes of CZP are provided for home administration at Weeks 6, 8, and 10. The subject has to return 1 syringe at the Week 12 Visit.
- Schedule appointment for next visit

8.4 Visits 5 and 6, and Visits 8 to 12 (Weeks 12, 24, 36, 48, 60, 72, and 84)

Assessments at these visits will include:

- Evaluation of uveitis flares that occurred since last visit
- Concomitant medications
- Vital signs (systolic and diastolic blood pressures)
- Physical examination (weight at Week 48 only) and extra-articular assessment (including the number of IBD exacerbations and number of psoriasis exacerbations [in subjects with concurrent psoriasis])
- Blood samples will be collected for
  - Hematology analyses
  - Biochemistry analyses
  - CRP testing
- Urine will be collected for urinalysis
- TB test for subjects with previously negative TB test result (Week 48 only)
- TB questionnaire
- Patient reported outcomes:
  - BASDAI
  - BASFI
  - ASQoL
  - ASAS HI questionnaire
  - SF-36
  - Total and nocturnal spinal pain
  - PtGADA
- PhGADA
- Swollen and tender joint counts
- AEs
- Contact IWRS to obtain CZP kit numbers
- Study drug administration onsite

- Provide subject with CZP for home administration Q2W until next scheduled site visit
- Schedule appointment for next visit

8.5 Visit 7 (Week 32)

Assessments at this visit will include:

- Evaluation of uveitis flares that occurred since last visit
- Concomitant medications
- Vital signs (systolic and diastolic blood pressure)
- CRP testing
- BASDAI
- PtGADA
- AEs
- Contact IWRS to obtain CZP kit numbers
- Study drug administration onsite
- Provide subjects with CZP for home administration Q2W until next scheduled site visit.
- Schedule appointment for next visit

8.6 Visit 13 (Week 96/Withdrawal Visit)

Assessments at this visit will include:

- Evaluation of uveitis flares that occurred since last visit
- Concomitant medications
- Vital signs (systolic and diastolic blood pressures)
- Physical examination (including weight) and extra-articular assessment (including the number of IBD exacerbations and number of psoriasis exacerbations [in subjects with concurrent psoriasis])
- Blood samples will be collected for
  - Hematology analyses
  - Biochemistry analyses
  - CRP testing
- Urine will be collected for
  - Urinalysis
  - Urine pregnancy test for women of childbearing potential
- TB test for subjects with previously negative TB test result
- TB questionnaire

- Patient reported outcomes
  - BASDAI
  - BASFI
  - ASQoL
  - ASAS HI questionnaire
  - SF-36
  - Total and nocturnal spinal pain
  - PtGADA
- PhGADA
- Swollen and tender joint counts
- AEs
- Contact IWRS to confirm Week 96/WD Visit
- Schedule appointment for next visit

8.7 Visit 14 (Follow-Up Visit)

The FU visit will occur 10 weeks after the final dose. Assessments at this visit will include:

- Concomitant medications
- Vital signs (systolic and diastolic blood pressures)
- Physical examination
- Urine dipstick pregnancy testing for women of childbearing potential
- AEs
- Contact IWRS to indicate that subject has completed the FU

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 depending on the presenting reason:

- Concomitant medications
- 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

9.1 Assessment of primary and secondary efficacy variables

9.1.1 Assessment of AU flares

Subjects will be requested to contact an ophthalmologist when they experience an AU flare at any time during the study. The ophthalmologist will confirm the AU flare and determine the duration, severity, and treatment. The ophthalmologist will be provided with documentation to ensure all protocol-requested information is collected. The documentation will inform the ophthalmologist about the subject's study participation and the requirements.

At each site visit, the subject will be questioned on the occurrence of uveitis flares since last visit. In case uveitis flares are confirmed by the subject the site will obtain the needed information from the ophthalmologist containing the diagnosis of AU, the affected eye, location of the uveitis in the affected eye, duration, severity, and treatment provided.

The following information will be collected:

- Start and end date of each AU flare (episode)
  - Start date: when subject experience first signs of the AU episode
  - End date: when treatment of the AU is stopped
- Grading
  - For uveitis flare, the highest grade noted during an episode of uveitis will be graded as follows:

    Grade 0=None; Grade 1+=Faint; Grade 2+=Moderate, iris and lens details clear; Grade3+=Marked, iris and lens details hazy; Grade4+=Intense, fibrin or plastic aqueous; ND=Not done or not assessed; UNK=Unknown
  - For cell count, the highest cell count noted during an episode of uveitis will be graded as follows:

    Grade 0=<1 cell; Grade 0.5+=1-5 cells; Grade 1+=6-15 cells; Grade 2+=16-25 cells; Grade 3+=26-50 cells; Grade 4+=>50 cells; ND=Not done or not assessed; UNK=Unknown
- Treatment

9.1.2 Ankylosing spondylitis disease activity score (ASDAS)

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

0.121 × [redacted] (BASDAI Question 2 result; see Section 9.1.3)

0.058 × [redacted] (BASDAI Question 6 result)

0.110 × PtGADA (see Section 9.1.7)

0.073 × [redacted] (BASDAI Question 3 result)

0.579 × (natural logarithm of the CRP [mg/L] + 1, see Week 32 in Table 5-1)

[redacted] PtGADA, [redacted] 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 ≥2.1, ≤3.5
- ASDAS-very High Disease activity: 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-Major Improvement: ASDAS reduction (improvement) of ≥2.0 relative to Baseline

The ASDAS will be calculated according to the assessment schedule in Table 5-1.

9.1.3 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, 2015; Garrett et al, 1994). The BASDAI is a validated self-reported instrument which consists of six 10-unit horizontal NRSs to measure [redacted] 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 visual analog scale (VAS) or 22.5% of the Baseline score (Pavy et al, 2005). An MCID of 1 unit will be selected for the NRS version (Appendix 16.4).

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

The BASDAI is calculated as follows:

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

[redacted] *item of the BASDAI*

[redacted] as a major symptom of AS can effectively be measured with single item questions such as the BASDAI item (van Tubergen et al, 2002). This item has shown moderate to good reliability and responsiveness (van Tubergen et al, 2002). The same MCID will be used for the [redacted] item of the BASDAI and 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.

9.1.4 ASAS20, ASAS40, ASAS5/6, and ASAS PR

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 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]:

- PtGADA (see Section 9.1.7)
- Pain assessment (the average of total and nocturnal spinal pain NRS scores)
- Function (represented by BASFI, Section 9.1.9)
- Inflammation (the mean of the BASDAI questions 5 and 6, [see Section 9.1.3] [redacted])

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 assessments per visit are described in the schedule of study assessments Table 5-1.

9.1.5 Physician's global assessment of disease activity (PhGADA)

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

9.1.6 Swollen and tender joint counts (44 joints evaluation)

The following 44 joints are to be examined for swelling and tenderness by the 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.

[redacted]

9.1.7 Patient's global assessment of disease activity (PtGADA) (NRS)

For the PtGADA questionnaire, subjects will score their global assessment of their disease activity in response to the question "How active was your spondylitis on average during the last week?" using a NRS where 0 is "not active" and 10 is "very active" (van Tubergen et al, 2015) (Appendix 16.5).

The PtGADA assessments per visit are described in the schedule of study assessments Table 5-1.

9.1.8 Total and nocturnal spinal pain NRS

The questionnaire for pain in the spine due to AS consists of 2 questions (ie, "How much pain of your spine due to spondylitis do you have?"; and "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) (Appendix 16.6).

The pain NRS assessments per visit are described in the schedule of study assessments Table 5-1.

9.1.9 Bath ankylosing spondylitis functional index (BASFI)

The BASFI is a validated disease-specific instrument for assessing physical function (van Tubergen et al, 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, 2002). 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 (Appendix 16.7).

The BASFI assessments per visit are described in the schedule of study assessments Table 5-1.

9.1.10 Extra-articular assessments

Extra-articular assessments (eg, number of IBD exacerbations and number of psoriasis exacerbations [in subjects with concurrent psoriasis]) are to be performed at Screening, Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, and at Completion at Week 96/WD Visit.

9.2 Assessment of other efficacy variables

9.2.1 Ankylosing spondylitis quality of life (ASQoL)

The ASQoL, a validated disease specific 18 item questionnaire, has been 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 (Appendix 16.8).

9.2.2 ASAS HI Questionnaire

The ASAS HI has been developed under the auspices of ASAS to assess health in subjects with all forms of SpA. The questionnaire contains 17 items measuring "functioning, disability and health" – a concept which is conceptualized in the International Classification of Functioning, Disability and Health. The International Classification of Functioning, Disability and Health, a model to systematically classify and describe functioning, disability, and health in human beings, has been used by ASAS as a basis to define a core set of items that are typical and relevant for subjects with AS. Based on this ICF core set for AS, an item pool has been developed containing various items which are linked to specific ICF categories including items related to functioning as well as environmental factors. The performance of the item pool has been tested and analyzed with Rasch Analysis. The best performing items have been included in the final measure. It can be used in clinical studies as a new composite index that captures relevant information on the health status of subjects with SpA (Klitz et al, 2015) (Appendix 16.9).

Each statement on the ASAS HI is given a score of 1=I agree OR 0=I do not agree. All item scores are summed up to give a total score that ranges from 0 (good functioning) to 17 (poor functioning).

It is to be noted that items 7 and 8 are not applicable for all subjects. For those subjects who ticked the response "not applicable," the sum score is analyzed based on n=16 or n=15, respectively.

Missing data:

A total score can be analyzed if no more than 20% of the data are missing. The total score is calculated as follows for respondents with 1 to a maximum of 3 missing responses:

Sumscore = $\frac{x}{17-m}$ X17 x=Item summation score

m=Number of missing items

Cases with more than 3 missing responses cannot be allocated a total score.

The ASAS HI questionnaire assessments per visit are described in Table 5-1.

9.2.3 Short-Form 36-Item Health Survey (SF-36)

The SF-36 (Version 2, standard recall) is a 36-item generic HRQoL instrument that uses a recall period of 4 weeks. Items are grouped into 8 domains as follows: Physical Functioning (10 items), Role Physical (4 items), Bodily Pain (2 items), General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role Emotional (3 items), Mental Health (5 items), and 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 Physical Component Summary and Mental Component Summary 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 SF-36 Version 2 manual (Ware et al,1994) states the following values: physical component summary, 2; mental component summary, 3; physical function, 3; role physical, 3; bodily pain, 3; general health, 2; vitality, 2; social functioning, 3; role emotional, 4; and mental health, 3 (Appendix 16.10).

The SF-36 has been used and has shown to be responsive in axSpA (van Tubergen et al, 2015; Haibel et al, 2008). The SF-36 will be administered per visit as described in the schedule of study assessments Table 5-1.

10 ASSESSMENT OF SAFETY

10.1 Adverse events

10.1.1 Definition of adverse event

An AE is any untoward medical occurrence in a subject 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 an IMP, whether or not related to the IMP.

To ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), 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.

10.1.2 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.

10.1.3 Description of adverse events

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

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

10.1.4 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.

10.1.5 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

10.1.6 Pregnancy

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately notify UCB's Drug Safety (DS) department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as 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.
- A Safety Follow-Up Visit should be scheduled 10 weeks after the subject has discontinued her IMP.

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

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 DS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow-up.

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

A pregnancy becomes a serious adverse event (SAE) in the following circumstances: miscarriage, abortion (elective or spontaneous), 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.

10.1.7 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the Study Drug Dosing module of the CRF. 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).

10.1.8 Safety signal detection

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

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

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

10.2 Serious adverse events

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

10.2.2 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 (FU Visit) for each subject, 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 IB and product information/SPC/Product Monographs, as applicable.

10.2.3 Follow up of serious adverse events

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

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

10.3 Adverse events of interest

An AE of interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

Adverse events of interest include:

- Serious infections including opportunistic infections
- Malignancies including lymphoma
- Demyelinating-like disorders
- Congestive heart failure
- 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)
- A confirmed LTBI must be reported as an AE of interest
- Confirmed active TB is an AE of interest. In the event that an active TB occurrence meets the protocol's SAE criteria, it is also an SAE.

Note : Potential Hy's Law, defined as ≥3xULN alanine aminotransferase or aspartate aminotransferase with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

10.4 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 10.3)

10.5 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 10.2.2.

Table 10–1: 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; RA=rheumatoid arthritis

[a] The lists of anticipated SAEs were based on the treatment-emergent SAEs with an incidence ≥0.5% in subjects who participated in UCB Sponsored placebo-controlled studies who received placebo (Crohn's disease and rheumatoid arthritis safety pooling).

10.6 Laboratory measurements

Hematology, biochemistry, and urinalysis samples will be taken at Screening, Baseline, Weeks 2, 4, 12, 24, 36, 48, 60, 72, 84, and 96/WD Visit. Testing for HBs-Ag, HBc-Ab, HBs-Ab, HCV-Ab, HIV, and HLA-B27 (if not yet known) will be performed at Screening.

- Hepatitis –associated disease markers

For all subjects, blood samples will be collected by qualified site personnel for the determination of the following:

- HBc-Ab
- HBs-Ag
- HBs-Ab
- HCV-Ab

These samples will be collected at the Screening Visit.

Hepatitis B virus deoxyribonucleic acid and hepatitis C virus ribonucleic acid are available as needed to assess the clinical status of subjects if required during the study.

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 10–2 lists the laboratory parameters that will be measured:

Table 10–2: Laboratory measurements

Hematology	Chemistry	Urinalysis	Others
Red blood cells	Sodium	pH	Hepatitis B surface antigen
Hemoglobin	Potassium	Protein	Antibodies to hepatitis C
Hematocrit	Chloride	Glucose	Antibodies to HIV
Platelets	Bicarbonate	Blood	HLA-B27
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	Glucose		
Eosinophils	Creatinine		
Basophils	Uric acid		
	Urea		
	Total protein		
	Albumin		
	Alkaline phosphatase		
	Aspartate aminotransferase		
	Alanine aminotransferase		
	Bilirubin		
	Total cholesterol		

CRP= C-reactive protein; HIV= human immunodeficiency virus; HLA-B27= human leukocyte antigen B27; RBC=red blood cell; WBC=white blood cell

10.6.1 Pregnancy testing

Pregnancy testing must be carried out for women of childbearing potential and will consist of serum testing at Screening, and urine dipstick testing at Baseline, Week 96/WD Visit, and FU Visit.

10.6.2 Physical assessments

A physical examination will be performed at Screening, Baseline, Weeks 2, 4, 12, 24, 36, 48, 60, 72, 84, 96/WD Visit, and at the FU Visit. 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, 96/WD Visit.

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

10.6.3 MRI assessments

Magnetic resonance imaging of the SIJs will be performed at the Screening Visit only. An MRI performed ≤3 months prior to the Baseline Visit may be used as the Baseline.

10.6.4 Tuberculosis assessments

10.6.4.1 Tuberculosis test

The IGRA test that will be used by the central laboratory is the QuantiFERON®-TB Gold In-Tube (QFT-GIT) test or updated version (QuantiFERON® Plus). The test results will be reported as positive, negative, or indeterminate and must be reviewed by an experienced TB specialist, radiologist, or a pulmonologist.

The TB test will be performed at the following timepoints:

- At Screening, all subjects will have a QuantiFERON-TB GOLD In-Tube test.
- At Week 48 and 96/WD Visit all subjects with a negative Quantiferon-TB GOLD In-Tube test at Screening will have the test repeated.

For subjects with a positive Quantiferon-TB GOLD In-Tube test at Screening, the test is not to be repeated at Weeks 48 and 96/WD Visit.

- Per the judgment of the Investigator, a QuantiFERON-TB GOLD In-Tube test can be performed at unscheduled visits at any time during the study.

  In case of an indeterminate result, a retest must be done shortly after, during the protocol-defined Screening window. If the test is positive or indeterminate on retest, the subject may not be randomized to IMP without further evaluation by a TB specialist. If LTBI is identified, appropriate treatment for TB prophylaxis and discussion with the study physician is required. If active TB is identified the subject cannot be randomized and is excluded from the study.

- At any other timepoint during the study if the IGRA test result is indeterminate, the IGRA must be reported once shortly after.

If during the study the assessment by IGRA is positive or indeterminate on retest for subjects who were previously negative at Screening and not treated for LTBI, the subject may not continue study treatment without further evaluation by a TB specialist and discussion with the Medical Monitor. If LTBI is identified, study treatment can only be re-initiated after prophylactic TB treatment is initiated. If active TB is identified, the subject must undergo appropriate study-specified withdrawal procedures.

Conditions for including LTBI subjects in the study:

- The Investigator must provide full documentation of the duration, and start and stop dates of LTBI treatments, and discuss with the study physician prior to allowing subject to screen (if the LTBI was discovered prior to subject screening) or prior to receiving study drug (if LTBI was identified at screening).
- Subjects who initiate treatment for LTBI during the Screening Period must repeat initial screening laboratory parameters, examination, and questionnaires (after receiving at least 4 weeks duration of treatment for LTBI) prior to randomization in the study, and must plan to continue the full course of LTBI prophylaxis therapy. The Investigator must assess that the subject's likelihood of completing the therapy is high and duly record his/her opinion in the subject's record prior to randomizing the subject. It is suggested to obtain the opinion of a TB specialist, especially for subjects having been in contact with multi-resistant TB.
- An extension of the Screening Period up to 12 weeks is allowed in order to allow for 8 weeks of LTBI treatment prior to study drug initiation. If the initial 8 weeks of prophylactic LTBI therapy cannot be accomplished with the extended Screening Period, the subject should be considered screen failed.

- Rescreening may occur only after discussion with and approval by the study physician (or Medical Monitor)

Procedure to be followed for subjects with conversion of IGRA or diagnosis of a new TB infection during the Study:

- Conversion is defined as a positive IGRA or 2 indeterminate results at the same visit (scheduled or unscheduled) of the same IGRA method.
- The subject should immediately discontinue study drug intake upon positive test conversion. Should evaluation of the subject by the appropriate TB specialist result in a diagnosis of LTBI, the study drug must be withheld until the appropriate prophylactic therapy has been received for at least 4 weeks and the subject is deemed likely to continue therapy to completion. The treatment must be discussed with the study physician before study drug is restarted.
- If the subject's evaluation reveals active TB infection during the course of 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 FU Visit as specified by the protocol.
- Refer to Section 10.4, for instructions on reporting a confirmed LTBI or confirmed active TB occurrence (note that in the event that an active TB occurrence meets the protocol-defined SAE criteria, it is also an SAE).

10.6.4.2 Chest x-ray

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).

Imaging must be read by an experienced TB imaging specialist, radiologist, pulmonologist or infectious disease specialist, who is specifically requested 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.

Additional chest x-ray or other imaging test should be performed when positive signs and symptoms indicate pulmonary infection, including potential TB infection, or when close exposure to persons with TB is documented.

10.6.4.3 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 completion at Week 96/WD Visit.

The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question [redacted] at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject

has latent or active TB (see Exclusion Criterion 24, Section 6.2). A "Yes" response to any of the questions during the study should trigger further assessments to determine whether the subject has either LTBI or active TB infection (Appendix 16.11).

Subjects with a LTBI must receive prophylactic therapy prior to continuing study medication.

Subjects with active TB infection must be withdrawn from the study and should be referred to a TB specialist for further assessments.

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 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 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 a measure, the Investigator must notify the Clinical Project Manager of the Sponsor within 24 hours and follow any local regulatory requirements.

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

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

11.2.1 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 CRFs 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.

Source documents that are computer generated and stored electronically must be printed for review by the monitor. 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 must be saved and stored as instructed by UCB (or its designee).

The following data will be recorded directly in the electronic patient reported outcome (ePRO) device (Section 11.3.2) on site and will not appear in a source document as defined above:

- Patient PROs: BASDAI, BASFI, ASQoL, ASAS HI questionnaire, SF-36, total and nocturnal spinal pain, and PtGADA,
- PhGADA and swollen and tender joint counts

11.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data should be 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 CRF should be supported by source documents, unless otherwise specified in Section 11.2.1.

11.3 Data handling

11.3.1 Case Report Form completion

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

This study will also use an electronic device (Site Tablet) to capture the ePRO questionnaires (see Section 11.3.2).

Serious adverse event reporting will be done using the SAE form (Section 10.2) 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.

11.3.2 Electronic reporting outcome

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

This study will use an electronic Site Tablet having a large screen and intuitive fingertip data entry to ensure all questionnaire data are captured appropriately, completely, and on time.

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

11.3.3 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. Case Report Form data are entered into the clinical database using independent, double-data entry, with the exception of comment fields, which are verified by a second person. In the event that the 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.

11.3.4 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.

11.4 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

11.5 Archiving and data retention

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

All essential documents should 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.

11.6 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).

11.7 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.

12 STATISTICS

A summary of statistical methods follows; more details will be provided in the Statistical Analysis Plan (SAP).

12.1 Definition of analysis sets

Two analysis sets are defined for this study:

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

Efficacy variables will be analyzed using the SS. In the unexpected case that subjects in the SS have an unknown incidence of AU flares for the prestudy period (ie, missing Baseline value for the primary efficacy variable), then a Full Analysis Set (FAS) would additionally be defined for efficacy analysis as all subjects in the SS with nonmissing Baseline value for the primary efficacy variable (ie, AU flare incidence data from prestudy period). In this situation, efficacy analysis would be conducted using the FAS rather than the SS.

Safety variables will be summarized using the SS.

12.2 General statistical considerations

In general, summary statistics (n [number of available measurements], arithmetic mean, SD, median, minimum, and maximum) for quantitative variable and frequency tables for qualitative data will be presented. As there is a single treatment arm in this study, all subjects will be presented together in a single treatment group (eg, as "All CZP" or similar).

Unless otherwise specified, the last valid measurement before study medication administration will be utilized as Baseline value.

All statistical analyses besides the primary efficacy analysis will be exploratory in nature only. Any p-values or confidence intervals produced in association with secondary or other analyses will be considered non-confirmatory.

The full details of the statistical analyses will be provided in the SAP. Any deviations from the final SAP as well as changes from the protocol will be detailed in the SAP and discussed in the Clinical Study Report.

All the analyses will be performed by using SAS Version 9.4 or above. The details regarding the presentation of statistical outputs will be provided in the SAP.

12.3 Planned efficacy analyses

12.3.1 Analysis of the primary efficacy variable

The primary efficacy analysis will consist of a comparison of the frequency of AU flares during the prestudy/historical period with that observed while in the study during CZP treatment. It is assumed that the frequency of AU flares follows a Poisson distribution. As such, the analysis will be performed as a generalized estimating equations analysis for Poisson outcome that will take into account the possible within-subject correlation (between the retrospective and prospective AU flare counts). The model will contain 2 records per subject corresponding to the frequency of AU flares before study and during the study, offset by log-time of each of the reporting periods. Disease duration will be included as a factor in the model, initially defined as <2 years and ≥2 years; the specific cutoffs for analysis may deviate from this based on the distribution seen in the data. The p-value for effect of CZP treatment on frequency of AU flares, along with rate ratio (CZP/historical) and 95% confidence interval, will be obtained from this model.

The above analysis will be repeated in the subgroup of subjects with at least 1 documented AU flare within 12 months prior to Baseline.

The primary efficacy analysis hypothesis will be tested based on significance level of alpha 0.05 and will be 2 sided. The entire alpha will be used for the primary efficacy analysis and analysis of the other secondary efficacy parameters will be supportive. Therefore, no alpha adjustment will be performed.

12.3.2 Other efficacy analyses

The AU flare rate (event rate) per 100 patient-years of exposure, both before and during the study, along with 95% confidence intervals (Garwood, 1936) will be presented as a key supportive analysis to the primary efficacy analysis results.

Other efficacy variables will be summarized by time point including change from Baseline or shift from Baseline, with descriptive statistics.

12.4 Planned safety analyses

12.4.1 Safety analyses

The frequency of all AEs will be presented 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.

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

12.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on study conduct, on the safety for an individual subject, or on the primary efficacy outcome for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate document. All the important

protocol violations will be tracked, although no analysis will be performed based on per protocol population.

12.6 Handling of dropouts or missing data

Analysis based on observed case and last observation carried forward for continuous variables or nonresponder imputation for categorical variables will be presented.

12.7 Planned interim analysis and data monitoring

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

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

An interim analysis is scheduled after the last subject has completed the Week 48 assessment. Details of the interim analysis will be included within the final SAP (or an interim SAP, if a separate SAP is needed specific to details of the interim analysis).

Although there is no intention to stop the study early due to efficacy or futility on the basis of these interim results, α=0.0001 will be spent in conjunction with this formal interim review of the data (Haybittle, 1971), and the final analysis of the primary efficacy variable will be conducted at the reduced 2-sided α-level of 0.049.

12.8 Determination of sample size

Based on results from a previous study with CZP in axSpA subjects (AS001), the AU flare rate while treated with CZP is estimated to be 14.6 events per 100 subject-years of exposure. Assuming the rate while treated with CZP represents a reduction in the flare rate of approximately 50%, the AU flare rate for the prestudy period prior to initiation of CZP is estimated to be 29.2 events per 100 subject-years of exposure. A conservative estimate of the sample size for this study is obtained via derivation of the per treatment-group sample size for Poisson regression based on the approach for a 2-group setting initially described by Signorini (1991) and implemented within SAS (Hu, 2008). Assuming an average follow-up period of 1.5 years with 2-sided α-level=0.049 for the final analysis of the primary efficacy variable, a sample size of N=86 subjects per treatment group will have 80% statistical power for a 2 group comparison, corresponding to a total sample size of N=86 subjects for this study with 1 treatment group. Due to the expected increase in statistical efficiency from the fact that each subject serves as his/her own control in the primary efficacy analysis, the actual power for this study is assumed to be >80 percent.

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 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.

Prior to participation in the study, the written ICF 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 ICF. As part of the consent process, each subject must consent to give direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the ICF 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 ICF by the IRB/IEC and use of the amended 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 ICF. A CRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

13.2 Subject identification cards

Upon signing the ICF, the subject or his/her 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.

13.3 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. Approval from the authorities should also be obtained before study initiation.

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.

13.4 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).

13.5 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.

14 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

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

15 REFERENCES

Barkham N, Keen HI, Coates LC, O'Connor P, Hensor E, Fraser AD, et al. Clinical and imaging efficacy of infliximab in HLA-B27-positive patients with magnetic resonance imaging-determined early sacroiliitis. Arthritis Rheum. 2009;60(4):946-54.

Boonen A, van der Heijde D, Landewé R, Guillemin F, Rutten-van Molken M, Dougados M, et al. Direct costs of ankylosing spondylitis and its determinants: an analysis among three European countries. Ann Rheum Dis. 2003;62:732-40.

Boonen A, van der Heijde D, Landewé R, Spoorenerg A, Schouten H, Rutten-van Molken M, et al. Work status and productivity costs due to ankylosing spondylitis: comparison of three European countries. Ann Rheum Dis. 2002;61:429-37.

Brandt J, Listing J, Sieper J, Rudwaleit M, van der Heijde D, Braun J. Development and preselection of criteria for short term improvement after anti-TNFα treatment in ankylosing spondylitis. Ann Rheum Dis. 2004;63:1438-44.

Braun J. Axial spondyloarthritis: thoughts about nomenclature and treatment targets. Clin Exp Rheumatol. 2012;30(4 Suppl 73):S132-5.

Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2011;70: 896-904.

Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007;369:1379-90.

Braun J, Zochling J, Baraliakos X, Alten R, Burmester G, Grasedyck K, et al. Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomised controlled trial. Ann Rheum Dis. 2006;65: 1147-1153.

Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994;21(12):2281-5.

Callhoff J, Sieper J, Weiß A, Zink A, Listing J. Efficacy of TNFα blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Ann Rheum Dis. 2015;74(6):1241-8.

Cantini F, Niccoli L, Cassara E, Kaloudi O, Nannini C: Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis: a randomized, prospective, long-term, follow-up study, Biologics. 2013:7 1-6.

CPMP/EWP/556/95 Rev. 2. Clinical investigation of medicinal products other than non-steroidal anti-inflammatory drugs (NSAIDs) for treatment of rheumatoid arthritis. Released for second consultation Jun 2015.

CPMP/ICH/135/95 Note for guidance on Good Clinical Practice (EMEA) Jul 2002.

Cuirea A, Scherer A, Exer P, Bernhard J, Dudler J, Beyeler B, et al. Tumor necrosis factor α inhibition in radiographic and nonradiographic axial spondyloarthritis: results from a large observational cohort. Arthritis Rheum. 2013;65:3096-106.

Davis Jr JC, Revicki D, van der Heijde DMF, Rentz AM, Wong RL, Kupper H, et al. Health-related quality of life outcomes in patients with active ankylosing spondylitis treated with adalimumab: results from a randomized controlled study. Arthritis Rheum. 2007;57(6):1050-7.

Dougados M, van der Heijde D, Sieper J, Braun J, Maksymowych W, Citera G, et al. Clinical and imaging efficacy of etanercept in early non-radiographic axial spondyloarthritis: a 12-week, randomised, double-blind, placebo-conrolled trial. OP0108, Anals Rheum Dis. 2013;72, Suppl 3:87.

Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum. 1991;34:1218-27.

Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, et al. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis. 2003;62(1):20-6.

Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008;9:105-21.

Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. Rheumatol Int. 2003;23:61-6.

Feldtkeller E, Bruckel J, Khan MA. Scientific contributions of ankylosing spondylitis patient advocacy groups. Curr Opin Rheumatol. 2000;12:239-247.

Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994;21(12):2286-91.

Garwood F. Fiducial limits for the Poisson distribution. Biometrika. 1936;28:437-42.

Haibel H, Brandt HC, Song IH, Brandt A, Listing J, Rudwaleit M, et al. No efficacy of subcutaneous methotrexate in active ankylosing spondylitis: a 16-week open-label trial. Ann Rheum Dis. 2007;66:419-21

Haibel H, Rudwaleit M, Braun J, Sieper J. Six months open label trial of leflunomide in active ankylosing spondylitis. Ann Rheum Dis. 2005;64:124-6.

Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. Arthritis Rheum. 2008;58(7):1981-91.

Haibel H, Heldmann F, Braun J, Listing J, Kupper H, Sieper J. Long-term efficacy of adalimumab after drug withdrawal and retreatment in patients with active non-radiographically evident axial pondyloarthritis who experience a flare. Arthritis Rheum. 2013;65(8):2211-3.

Haybittle JL. Repeated assessments of results in clinical trials of cancer treatment. Brit. J. Radiol. 1971. 44 (526):793-7.

Hu K. Sample Size Estimation for Trials of Recurrent Events. Amgen Inc. 2008. 1-8.

Huscher D, Merkesdal S, Thiele K, Zeidler H, Schneider M, Zink A. Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. Ann Rheum Dis. 2006;65:1175-1183.

Klitz U, van der Heijde D, Boonen A, Cieza A, Stucki G, Khan MA, et al. Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. Ann Rheum Dis. 2015;830-5

Kobelt G, Andlin-Sobocki P, Brophy S, Jonsson L, Calin A, Braun J. The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade). Rheumatology. 2004;43:1158-66.

Landewé R, Braun J, Deodhar A, Dougados M, Maksymowch P, Mease P, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis. 2014; 73: 39-47.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-12.

Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68(1):18-24.

Meikle AW and Tyler FH. Potency and duration of action of glucocorticoids. Effects of hydrocortisone prednisone and dexamethasone on human pituitary-adrenal function. Am J Med 1977;63;200-7

Mielants H, Veys EM, Cuvelier C, De Vos M, Goemaere S, De Clercq L, et al. The evolution of spondyloarthropathies in relation to gut histology. II. Histological aspects. J Rheumatol. 1995;22(12):2273-8.

Monnet D, Breban M, Hudry C, Dougados M, Brézin AP. Ophthalmic findings and frequency of extraocular manifestations in patients with HLA-B27 uveitis: a study of 175 cases. Ophthalmology. 2004;111:802-9.

Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum. 2010;62:1576-82.

Olivieri I, D'Angelo S, Padula A, Leccese P, Nigro P, Palazzi C. Can we reduce the dosage of biologics in spondyloarthritis?, Autoimmun Rev. 2013; 12: 691-3.

Pavy S, Brophy S, Calin A. Establishment of the minimum clinically important difference for the bath ankylosing spondylitis indices: a prospective study. J Rheumatol. 2005;32(1):80-5.

Poddubnyy D. Axial spondyloarthritis: is there a treatment of choice? Ther Adv Musculoskelet Dis. 2013;5:45-54

Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Märker-Hermann E, Zeidler H, et al. Effect of non-steroidal anti-inflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. Ann Rheum Dis. 2012;71:1616-22.

Rosenbaum JT, Suhler EB, Lin P. The future of uveitis treatment. Opthamolology. 2014;121(1):365-76

Rosenbaum JT. Characterization of uveitis associated with spondyloarthritis. J Rheumatol. 1989;16:792-6.

Rostom S, Dougados M, Gossec L. New tools for diagnosing spondyloarthropathy. Joint Bone Spine. 2010;77:108-14.

Rudwaleit M, Sieper J. Referral strategies for early diagnosis of axial spondyloarthritis. Nat Rev Rheumatol. 2012;8:262-8.

Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70:25-31.

Rudwaleit M. New approaches to diagnosis and classification of axial and peripheral spondyloarthritis. Curr Opin Rheumatol. 2010;22:375-80.

Rudwaleit M, Haibel H, Baraliakos X, Listing J, Märker-Hermann E, Zeidler H, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum. 2009a;60:717-27.

Rudwaleit M, Landewe R, van der Heijde D, Listing J, Brandt J, Braun J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis. 2009b;68:770-6.

Rudwaleit M, Landewé R, van der Heijde D, Listing K, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009c;68:777-83.

Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? Arthritis Rheum. 2005;52:1000-8.

Sieper J, van der Heijde D. Review: Nonradiographic axial spondyloarthritis: new definition of an old disease? Arthritis Rheum. 2013;65:543-51.

Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009;68(Suppl 2):ii1-ii44.

Signorini DF. Sample size for Poisson regression. Biometrika. 1991. 78:446-50.

van der Heijde D, Dougados M, Davis J, Weisman MH, Maksymowych W, Braun J, et al. Assessment in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. Arthritis Rheum. 2005;52(2):386-94.

van der Heijde D, Schiff MH, Sieper J, Kivitz A, Wong RL, Kupper H, et al. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. Ann Rheum Dis. 2009;68:922-9.

van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361-8.

van Denderen JC, Visman IM, Nurmohamed MT, Suttorp-Schulten MS, van der Horst-Bruinsma IE. Adalimumab significantly reduces the recurrence rate of anterior uveitis in patients with Ankylosing Spondylitis. J Rheumatol. 2014 Sep;41(9):1843-8.

van Praet L, van den Bosch FE, Jacques P, Carron P, Jans L, Colman R, et al. Microscopic gut inflammation in axial spondyloarthritis: a multiparametric predictive model. Ann Rheum Dis. 2013;72(3):414-7.

van Tubergen A, Black PM, Coteur G. Are patient-reported outcome instruments for ankylosing spondylitis fit for purpose for the axial spondyloarthritis patient? A Qualitative and Psychometric Analysis. Rheumatology. 2015; 54(10):1842-51.

van Tubergen A, Debats I, Ryser L, Londoño J, Burgos-Vargas R, Cardiel MH, et al. Use of a numerical rating scale as an answer modality in ankylosing spondylitis-specific questionnaires. Arthritis Rheum. 2002;47(3):242-8.

Wakefield D, Chang JH. Epidemiology of uveitis. Int Ophthalmol Clin. 2005;45(2):1-13.

Ware JE, Kosinski M, Keller SD. SF-36 Physical and Mental Health Summary scales: a user's manual. 1994. Maruish, M. E. (Ed.) 2011.

Zeboulon N, Dougados M, Gossec L. Prevalence and characteristics of uveitis in the spondyloarthropathies: a systematic literature review. Ann Rheum Dis. 2008;67:955-9.

16 APPENDICES

16.1 Modified NY criteria for ankylosing spondylitis

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

Modified NY criteria for ankylosing spondylitis

Diagnosis
1) Clinical criteria
a) Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest.
b) Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
c) Limitation of chest expansion relative to normal values corrected for age and sex.
2) Radiologic criterion
Sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3 to 4 unilaterally.
Grading
1) Definite ankylosing spondylitis if the radiologic criterion is associated with at least 1 clinical criterion

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

16.2 ASAS classification criteria for axSpA

ASAS classification criteria for axSpA (for subjects with chronic back pain ≥3 months and age at onset <45 years)	
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]	Psoriasis
Arthritis	Crohn's disease/ulcerative colitis
Enthesitis (heel)	Good response to NSAIDs
Uveitis	Family history for SpA
Dactylitis	HLA-B27
	Elevated CRP

ASAS=Assessment of SpondyloArthritis international Society; axSpA=axial spondyloarthritis; 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 <40 years
2) Insidious onset
3) Improvement with exercise
4) No improvement with rest
5) Pain at night (with improvement upon getting up)

16.3 Corticosteroid equivalent doses

Table 16–1: Corticosteroid equivalent doses (with reference to prednisone 10mg dose) (Meikle and Tyler, 1977)

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

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

16.5 PtGADA (NRS)

NRS patient global disease activity

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

Please tick the box that represents your answer (ie, ☒ 10)

0	1	2	3	4	5	6	7	8	9	10

Not active very active

16.6 Total spinal pain NRS and nocturnal spinal pain NRS

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

1. Total SpinePain
How much pain of your spine due to spondyloarthritis do you have?

0	1	2	3	4	5	6	7	8	9	10

no pain — most severe pain

2. Nocturnal SpinePain
How much pain of your spine due to spondyloarthritis do you have at night?

0	1	2	3	4	5	6	7	8	9	10

no pain — most severe pain

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

16.9 ASAS Health Index Questionnaire

ASAS Health Index

Name:
Date:

Please answer all statements by placing one check mark per statement to indicate which response best applies to you **at this moment in time** taking into account your rheumatic disease (the term “rheumatic disease” contains all forms of spondyloarthritis including ankylosing spondylitis) .

1. Pain sometimes disrupts my normal activities.
   - ☐ I agree
   - ☐ I do not agree
2. I find it hard to stand for long.
   - ☐ I agree
   - ☐ I do not agree
3. I have problems running.
   - ☐ I agree
   - ☐ I do not agree
4. I have problems using toilet facilities.
   - ☐ I agree
   - ☐ I do not agree
5. I am often exhausted.
   - ☐ I agree
   - ☐ I do not agree
6. I am less motivated to do anything that requires physical effort.
   - ☐ I agree
   - ☐ I do not agree
7. I have lost interest in sex.
   - ☐ I agree

☐ I do not agree

☐ Not applicable, I do not want to answer

8. I have difficulty operating the pedals in my car.

☐ I agree

☐ I do not agree

☐ Not applicable, I cannot / do not drive

9. I am finding it hard to make contact with people.

☐ I agree

☐ I do not agree

10. I am not able to walk outdoors on flat ground.

☐ I agree

☐ I do not agree

11. I find it hard to concentrate.

☐ I agree

☐ I do not agree

12. I am restricted in traveling because of my mobility.

☐ I agree

☐ I do not agree

13. I often get frustrated.

☐ I agree

☐ I do not agree

14. I find it difficult to wash my hair.

☐ I agree

☐ I do not agree

15. I have experienced financial changes because of my rheumatic disease.

☐ I agree

☐ I do not agree

16. I sleep badly at night.

☐ I agree

☐ I do not agree

ASAS Health Index

17. I cannot overcome my difficulties.

☐ I agree

☐ I do not agree.

Thank you for answering this questionnaire

Environmental factors related to ASAS Health Index

Date: _____
Name: _____

Please answer all statements by placing one check mark per statement to indicate which response best applies to you **at this moment in time** taking into account your rheumatic disease (the term "rheumatic disease" contains all forms of spondyloarthritis including ankylosing spondylitis).

As a result of my rheumatic disease, my family / relatives take more responsibility for household tasks.

☐ I agree

☐ I do not agree

I don't like the way my friends act around me.

☐ I agree

☐ I do not agree

I cannot count on my relatives to help me with my problems.

☐ I agree

☐ I do not agree

I modify my home and work environments.

☐ I agree

☐ I do not agree

I have difficulties getting worsening of my disease acknowledged by a health care professional.

☐ I agree

☐ I do not agree

Treatment of my rheumatic disease is taking up time.

☐ I agree

☐ I do not agree

My friends expect too much of me.

☐ I agree

☐ I do not agree

No one pays much attention to me at home.

☐ I agree

☐ I do not agree

My friends understand me.

☐ I agree

☐ I do not agree

Thank you for answering this questionnaire

Developed by **A**ssessment of **S**pondylo**A**rthritis International **S**ociety (ASAS)

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17 APPENDICES

17.1 Protocol Amendment 1

Rationale for the amendment

The purpose of this non-substantial amendment is to clarify the Screening requirement for MRI and history of tobacco use, and to incorporate the administration of IMP at Week 32.

Modifications and changes

Global changes

Magnetic resonance imaging of the spine at Screening is not required for this study. An MRI of the SIJs will be performed during the Screening Period, or an MRI of the SIJs performed ≤3 months prior to the Baseline Visit may be used as the Baseline.

The IMP will be administered onsite at Visit 7 (Week 32).

Specific changes

Change #1

Table 5-1: Schedule of assessments

Row 4

Medical history (including axSpA history) and concomitant diseases

Has been changed to:

Medical history (including axSpA history, and tobacco use) and concomitant diseases

Change #2

Table 5-1: Schedule of assessments

Row 29

"Study drug sc injections" has been checked for Visit 7 (Week 32).

Change #3

Table 5-1: Schedule of assessments

Footnote k

Magnetic resonance imaging of the spine and SIJs to be performed during the Screening Period. An MRI performed ≤3 months prior to the Baseline Visit may be used as the Baseline.

Has been changed to:

Magnetic resonance imaging of the SIJs to be performed during the Screening Period. An MRI performed ≤3 months prior to the Baseline Visit may be used as the Baseline.

Change #4

Section 8.1 Visit 1 (Week -5 to -1) Screening

Bullet point 5

- Significant past medical and procedure history and concomitant disease (including axSpA history)

Has been changed to:

- Significant past medical and procedure history (including tobacco use) and concomitant disease (including axSpA history)

Change #5

Section 8.1 Visit 1 (Week -5 to -1) Screening

Bullet point 17

- MRI evaluation of the spine and SIJ. An MRI performed ≤3 months prior to the Baseline Visit may be used for assessing the eligibility at Baseline.

Has been changed to:

- MRI evaluation of the SIJ. An MRI performed ≤3 months prior to the Baseline Visit may be used for assessing the eligibility at Baseline.

Change #6

Section 8.5 Visit 7 (Week 32)

Bullet point 9 has been added:

- Study drug administration onsite

Change #7

Section 10.6.3 MRI assessments

Magnetic resonance imaging of the spine and SIJs will be performed at the Screening Visit only. An MRI performed ≤3 months prior to the Baseline Visit may be used as the Baseline.

Has been changed to:

Magnetic resonance imaging of the SIJs will be performed at the Screening Visit only. An MRI performed ≤3 months prior to the Baseline Visit may be used as the Baseline.

17.2 Protocol Amendment 2

Rationale for the amendment

The main purpose of this substantial amendment is to provide clarification on magnetic resonance imaging (MRI) and x-ray assessments. In addition, text was added to the protocol about information collected for the assessment of AU flares and about Hy's Law cases, and other minor updates/clarifications were also done to the protocol (see global changes below). Details of each specific change are provided below.

Modifications and changes

Global changes

- Clarification has been added that if no chest x-ray is available within the 3 months prior to Screening, the x-ray can be done during the Screening Period. If the modified New York (mNY) classification criteria were met in the x-ray performed prior to Screening, the x-ray is not to be repeated.
- Clarification has been added that an MRI assessment is not needed for subjects with AS and that AS subjects must have evidence of sacroiliitis on x-ray taken prior to Baseline meeting the mNY classification criteria according to the Investigator.
- Minor updates have been made to ophthalmic exclusion criteria and prior concomitant medications exclusion table.
- Minor edits have been made to text about storage conditions at the site.
- Details about the information collected for the assessment of AU flares have been added to the protocol.
- Text about Hy's Law cases has been added to the Adverse Events of Interest section.
- Minor corrections have been done to the table in Appendix 16.2.
- Minor editorial and format corrections have been done to the protocol.

Specific changes

Change #1

Table 5-1: Schedule of assessments

Row 17

MRI[k]

Has been changed to:

MRI (nr-axSpA subjects only)[k]

Change #2

Table 5-1: Schedule of assessments

Row 18 has been added and checked for Period 1 Screening Visit:

X-ray (AS subjects only)[l]

Change #3

Table 5-1: Schedule of assessments, footnote i

[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).

Has been changed to:

[i] Chest x-ray used for screening must have been done within 3 months prior to the 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). If no chest x-ray is available within the 3 months prior to the Screening Visit, the x-ray can be done during the Screening Period.

Change #4

Table 5-1: Schedule of assessments, footnote k

[k] Magnetic resonance imaging of the SIJs to be performed during the Screening Period. An MRI performed ≤3 months prior to the Baseline Visit may be used as the Baseline.

Has been changed to:

[k] For subjects with nr-axSpA, an MRI of the SIJs is to be performed during the Screening Period. An MRI performed ≤3 months prior to the Baseline Visit may be used as the Baseline. An MRI assessment is not needed for patients with AS.

Change #5

Table 5-1: Schedule of assessments, new footnote l

Footnote l has been added (for new Row 18 and former footnote l has been renumbered to footnote m):

[l] AS subjects must have evidence of sacroiliitis on x-ray taken prior to Baseline meeting the mNY classification criteria according to the Investigator. If not available, this x-ray is to be taken during the Screening Period. If an x-ray was performed prior to the Screening Visit and the mNY classification criteria were met, the x-ray is not to be repeated.

Change #6

Section 6.1 Inclusion Criteria

Inclusion criterion 6, bullets 3 and 4

- Nr-axSpA subjects must either have CRP > upper limit of normal (ULN) and/or current evidence of sacroiliitis on MRI taken within 3 months prior to Baseline (no confirmation by central reading) as defined by ASAS criteria
- AS subjects must have evidence of sacroiliitis on x-ray taken within 12 months prior to Baseline meeting mNY criteria according to the Investigator

Have been changed to:

- Nr-axSpA subjects must either have CRP > upper limit of normal (ULN) and/or current evidence of sacroiliitis on MRI (no confirmation by central reading) as defined by ASAS criteria
- AS subjects must have evidence of sacroiliitis on x-ray meeting the mNY classification criteria according to the Investigator

Change #7

Section 6.2 Exclusion Criteria

Ophthalmic exclusion criteria

Exclusion criterion 9

10.9. Any condition or complicating factor that may interfere with the AU assessment, for example:

a. Intraocular pressure of ≥25 mmHg
b. Corneal or lens opacity
c. Proliferative or severe nonproliferative diabetic retinopathy or clinically significant macular edema due to diabetic retinopathy
d. Neovascular/wet age-related macular degeneration
e. History of scleritis

Has been changed to:

11. 9. Any condition or complicating factor that may interfere with the AU assessment, for example:

a. History of cataract surgery within 6 months prior to Baseline
b. Corneal or lens opacity
c. Proliferative or severe nonproliferative diabetic retinopathy or clinically significant macular edema due to diabetic retinopathy
d. Neovascular/wet age-related macular degeneration

e. History of scleritis

f. History of intraocular surgery, with the exception of phacoemulsification

Change #8

Exclusion criterion 16

Table 6-1: Concomitant Medications (Prior to Baseline and Study Visits)

Rows 8, 9, and 10:

Table 6-1: Concomitant Medications (Prior to Baseline and Study Visits)		
Drug class	**Dose**	**Exclusion criteria**
DMARDs: hydroxychloroquine (HCQ) and/or methotrexate (MTX)	Maximum allowed: HCQ ≤400mg daily MTX ≤25mg weekly	Use initiated in and/or any change in the dose regimen in the 28 days prior to the Baseline Visit is exclusionary. DMARDs dose should be kept stable throughout the study except for reasons of intolerance, where the DMARD dose may be decreased but not discontinued.
DMARDs: sulfasalazine (SSZ), azathioprine, cyclosporine, cyclophosphamide, mycophenolic acid, apremilast	Any dose	Use within 28 days prior to the Baseline Visit is exclusionary. Must not be started during the study.
DMARDs: leflunomide	Any dose	Use in the 6 months prior to the Baseline Visit is exclusionary unless a cholestyramine washout has been performed. In case of a cholestryramine washout, use 28 days prior to the Baseline Visit is acceptable. Must not be started during the study.

Have been changed to:

Table 6-1: Concomitant Medications (Prior to Baseline and Study Visits)		
Drug class	**Dose**	**Exclusion criteria**
Disease-modifying antirheumatic drugs (DMARDs): sulfasalazine (SSZ) and/or hydroxychloroquine (HCQ) and/or methotrexate (MTX) and/or leflunomide (LFN) and/or azathioprine (AZA)	Maximum allowed: SSZ ≤3g daily HCQ ≤400mg daily MTX ≤25mg weekly AZA ≤150mg daily LFN ≤20mg daily	Use initiated in and/or any change in the dose regimen in the 28 days prior to the Baseline Visit is exclusionary. DMARDs dose should be kept stable throughout the study except for reasons of intolerance, where the DMARD dose may be decreased.
DMARDs: cyclosporine, cyclophosphamide, mycophenolic acid, apremilast	Any dose	Use within 28 days prior to the Baseline Visit is exclusionary. Must not be started during the study.

Change #9

Section 7.5.1 Storage at the site

Paragraph 3

Appropriate storage conditions must be ensured by both controlled room temperature and completion of a temperature log in accordance with local requirements on a regular basis (eg, once a week), but at least once per working day showing minimum and maximum temperatures reached over the time interval. In case of an out of range temperature, based on discussion with a UCB Quality Assurance representative, the Drug Supply Coordinator will then provide the site with instructions regarding use of the IMP and adjust the status of the IMP as needed in the IWRS.

Has been changed to:

Appropriate storage conditions (storage of CZP is to be done at 2 to 8ºC) must be ensured and completion of a temperature log in accordance with local requirements must be done on a regular basis (eg, once a week), but at least once per working day showing minimum and maximum temperatures reached over the time interval. In case of an out of range temperature, based on discussion with a UCB Quality Assurance representative, the Drug Supply Coordinator will then provide the site with instructions regarding use of the IMP and adjust the status of the IMP as needed in the IWRS.

Change #10

Section 8.1 Visit 1 (Week -5 to -1) Screening

Bullet 17

- MRI evaluation of the SIJ. An MRI performed ≤3 months prior to the Baseline Visit may be used for assessing the eligibility at Baseline.

Has been changed to:

- For subjects with nr-axSpA, an MRI of the SIJs is to be performed during the Screening Period. An MRI performed ≤3 months prior to the Baseline Visit may be used as the Baseline. An MRI assessment is not needed for patients with AS.

And the following bullets have been added above and below Bullet 17:

- Chest x-ray used for screening must have been done within 3 months prior to the 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). If no chest x-ray is available within the 3 months prior to the Screening Visit, the x-ray can be done during the Screening Period.
- AS subjects must have evidence of sacroiliitis on x-ray taken prior to Baseline meeting the mNY classification criteria according to the Investigator. If not available, this x-ray is to be taken during the Screening Period. If an x-ray was performed prior to the Screening Visit and the mNY classification criteria were met, the x-ray is not to be repeated.

Change #11

Section 9.1.1 Assessment of AU flares

Subjects will be requested to contact their ophthalmologist when they experience an AU flare at any time during the study. The ophthalmologist will confirm the AU flare and determine the duration, severity, and treatment. The subject's ophthalmologist will be provided with documentation to ensure all protocol-requested information is collected. The documentation will inform the subject's ophthalmologist about the subject's study participation and the requirements.

At each site visit, the subject will be questioned on the occurrence of uveitis flares since last visit. In case uveitis flares are confirmed by the subject the site will obtain the needed information from the subject's ophthalmologist containing the diagnosis of AU, the affected eye, location of the uveitis in the affected eye, duration, severity, and treatment provided.

Has been changed to:

Subjects will be requested to contact an ophthalmologist when they experience an AU flare at any time during the study. The ophthalmologist will confirm the AU flare and determine the duration, severity, and treatment. The ophthalmologist will be provided with documentation to ensure all protocol-requested information is collected. The documentation will inform the ophthalmologist about the subject's study participation and the requirements.

At each site visit, the subject will be questioned on the occurrence of uveitis flares since last visit. In case uveitis flares are confirmed by the subject the site will obtain the needed information from the ophthalmologist containing the diagnosis of AU, the affected eye, location of the uveitis in the affected eye, duration, severity, and treatment provided.

The following information will be collected:

- Start and end date of each AU flare (episode)
  - Start date: when subject experience first signs of the AU episode
  - End date: when treatment of the AU is stopped
- Grading
  - For uveitis flare, the highest grade noted during an episode of uveitis will be graded as follows:

    Grade 0=None; Grade 1+=Faint; Grade 2+=Moderate, iris and lens details clear; Grade3+=Marked, iris and lens details hazy; Grade4+=Intense, fibrin or plastic aqueous; ND=Not done or not assessed; UNK=Unknown
  - For cell count, the highest cell count noted during an episode of uveitis will be graded as follows:

    Grade 0=<1 cell; Grade 0.5+=1-5 cells; Grade 1+=6-15 cells; Grade 2+=16-25 cells; Grade 3+=26-50 cells; Grade 4+=>50 cells; ND=Not done or not assessed; UNK=Unknown
- Treatment

Change #12

Section 10.3 Adverse events of interest

The following text has been added as last paragraph:

Note : Potential Hy's Law, defined as ≥3xULN alanine aminotransferase or aspartate aminotransferase with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

Change #13

Appendix 16.2 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]	Psoriasis
Arthritis	Crohn's disease/ulcerative colitis
Enthesitis (heel)	Good response to NSAIDs
Uveitis	Family history for SpA
Dactylitis	HLA-B27
	Elevated CRP

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

[*] Active inflammatory lesions of sacroiliac joints with definite bone marrow oedema/osteitis suggestive of sacroiliitis associated with spondyloarthritis in MRI or radiographic sacroiliitis Grade 2 to 4 bilaterally or grade 3 to 4 unilaterally according to modified NY criteria.

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

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

1) Age at onset <40 years
2) Insidious onset
3) Improvement with exercise
4) No improvement with rest
5) Pain at night (with improvement upon getting up)

Has been changed to:

ASAS classification criteria for axSpA (for subjects with chronic back pain ≥3 months and age at onset <45 years)	
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]	Psoriasis
Arthritis	Crohn's disease/ulcerative colitis
Enthesitis (heel)	Good response to NSAIDs
Uveitis	Family history for SpA
Dactylitis	HLA-B27
	Elevated CRP

ASAS=Assessment of SpondyloArthritis international Society; axSpA=axial spondyloarthritis; 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 <40 years
2) Insidious onset
3) Improvement with exercise
4) No improvement with rest
5) Pain at night (with improvement upon getting up)

17.3 Protocol Amendment 3

Rationale for the amendment

The purpose of this non-substantial amendment is to update the safety variables as a secondary safety variable and other safety variables.

Modifications and changes

Global changes

- Updates have been made to the safety variables to include TEAEs as a secondary safety variable and blood pressure, physician examination, and clinical laboratory values as other safety variables.
- Study contact information was updated.
- Minor editorial and format corrections have been done to the protocol.

Specific changes

Change #1

Study Contact Information

Clinical Trial Biostatistician

Name:	[redacted], MS
Address:	UCB Biosciences, Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 USA
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Clinical Trial Biostatistician

Name:	Dr. [redacted]
Address:	UCB Biosciences GmbH Alfred-Nobel-Strasse 10 40789 Monheim Germany
Phone:	[redacted]
Fax:	[redacted]

Change #2

Section 4.2: Safety variables

Safety variables to be assessed are:

- Adverse events (AEs)
- Blood pressure
- Physical examination
- Clinical laboratory values (hematology, biochemistry, and urinalysis)

Has been changed to:

Section 4.2: Safety variables

Section 4.2.1: Secondary safety variable

The secondary safety variable to be assessed is treatment-emergent adverse events (TEAEs).

Section 4.2.2: Other safety variables

The following other safety variables to be assessed are:

- Blood pressure
- Physical examination
- Clinical laboratory values (hematology, biochemistry, and urinalysis)

18 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

19 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.

Approval Signatures

Name: as0007-protocol-amend-3

Version: 1.0

Document Number: CLIN-000148098

Title: AS0007 Protocol Amendment 3

Approved Date: 27 Jan 2020

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 26-Jan-2020 15:35:31 GMT+0000
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Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 27-Jan-2020 09:34:22 GMT+0000