NONINTERVENTIONAL STUDY

OBSERVATIONAL PLAN AS0002 AMENDMENT 1

A NONINTERVENTIONAL STUDY TO ASSESS THE EFFECTIVENESS OF CERTOLIZUMAB PEGOL IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS IN DAILY PRACTICE

UCB BIOPHARMA SPRL

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<td>ADR</td>
<td>adverse drug reaction</td>
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<tr>
<td>AE</td>
<td>adverse event</td>
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<tr>
<td>AS</td>
<td>ankylosing spondylitis</td>
</tr>
<tr>
<td>ASAS</td>
<td>Assessment of SpondyloArthritis International Society</td>
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<td>Assessment of SpondyloArthritis International Society 20%, 40% response criteria</td>
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<td>ASDAS</td>
<td>Ankylosing Spondylitis Disease Activity Score</td>
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<tr>
<td>axSpA</td>
<td>axial spondyloarthritis</td>
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<tr>
<td>BASDAI</td>
<td>Bath Ankylosing Spondylitis Disease Activity Index</td>
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<tr>
<td>BASFI</td>
<td>Bath Ankylosing Spondylitis Functional Index</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>CV</td>
<td>coefficient of variation</td>
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<tr>
<td>CZP</td>
<td>certolizumab pegol</td>
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<tr>
<td>DMARD</td>
<td>disease-modifying antirheumatic drug</td>
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<td>DS</td>
<td>Drug Safety</td>
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<td>eDF</td>
<td>electronic Documentation form</td>
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<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
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<td>FAS</td>
<td>Full Analysis Set</td>
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<td>MedDRA®</td>
<td>Medical Dictionary for Regulatory Activities</td>
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<td>mNY</td>
<td>modified New York</td>
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<td>MRI</td>
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<td>NIS</td>
<td>noninterventional study</td>
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<td>nr-axSpA</td>
<td>nonradiographic axial spondyloarthritis</td>
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<tr>
<td>NRS</td>
<td>Numeric Rating Scale</td>
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<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
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<td>Patient Data Consent form</td>
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<td>Physician’s Global Assessment of Disease Activity</td>
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<td>Patient’s Global Assessment of Disease Activity</td>
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<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
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<tr>
<td>SD</td>
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<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<td>spondyloarthritis</td>
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<td>TNF</td>
<td>tumor necrosis factor</td>
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1 RATIONALE FOR THE STUDY

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.

The Assessment of SpondyloArthritis International Society (ASAS) working group has established classification criteria to distinguish 2 broad categories of SpA: peripheral SpA, which includes diseases affecting mainly peripheral joints, such as reactive arthritis and psoriatic arthritis, and axial SpA (axSpA), which comprises diseases with mainly axial involvement (sacroiliac joints and spine), including ankylosing spondylitis (AS) and nonradiographic axSpA (nr-axSpA) (Rudwaleit et al, 2011; Rudwaleit, 2010; Rudwaleit et al, 2009b; Rudwaleit et al, 2009c).

The main clinical symptom of axSpA is inflammatory back pain. In most patients the disease typically originates in the sacroiliac joints, then, may progress to the spine. In the sacroiliac joints and the spine, active inflammation results in erosions, sclerosis, and fatty lesions. However, the most characteristic feature is new bone formation leading to ankylosis of the sacroiliac joints and syndesmophytes in the spine. As a result of extended syndesmophyte formation, the spine may become fused over time (Braun, 2012; Rudwaleit et al, 2009a).

Axial SpA encompasses the full spectrum of axial disease, with AS and nr-axSpA as opposite ends of the spectrum (Braun, 2012; Rudwaleit et al, 2009a; Rudwaleit et al, 2005). Patients with AS have definitive evidence of structural changes in the sacroiliac joint (sacroilitis) on conventional radiographs, normally fulfilling the modified New York (mNY) criteria (van der Linden et al, 1984), whereas those with nr-axSpA have little or no definitive structural changes on conventional radiographs (Rudwaleit et al, 2005; Dougados et al, 1991).

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

Axial SpA impacts a substantial proportion of the population. Limited information on the epidemiology of axSpA exists. Recent data suggest that the prevalence of axSpA in the USA is similar to that of rheumatoid arthritis (axSpA: 0.7% to 1.4%; rheumatoid arthritis: 0.5% to 1.0%) (Reveille et al, 2012; Myasoedova et al, 2010; Helmick et al, 2008). In Europe, the prevalence of AS ranges between 0.08 and 0.55% (Anagnostopoulos et al, 2010; Akkoc and Khan, 2005; Saraux et al, 2005). In a recent study, the prevalence of axSpA was estimated to be 3 to 4 times higher than the prevalence of AS (Bakland and Nossent, 2013).

Axial SpA typically presents in patients below 45 years of age, and these relatively young and otherwise healthy patients face a significant disease burden regardless of whether or not they have definitive evidence of sacroilitis on x-ray (Callhoff et al, 2014; Landewé et al, 2014; Cuirea et al, 2013).
Patients with AS experience substantial pain, severe stiffness of all joints lasting several hours, substantial sleep disturbances, reduced mobility and overall function, reduced quality of life, loss of productivity, and other disease-related symptoms (Huscher et al, 2006; Kobelt et al, 2006; Kobelt et al, 2004; Boonen et al, 2003; Boonen et al, 2002; Ward, 2002). Disability is related to both the degree of inflammatory activity and the degree of bony ankylosis.

The diagnosis of axSpA is based on laboratory and clinical assessments, considering typical signs and symptoms but also excluding other diseases that appear more likely:

- **History:** age of onset, back pain at night, disturbed sleep, morning stiffness, and peripheral symptoms such as swelling and tenderness of joints, uveitis, enthesitis, arthritis, colitis, and psoriasis
- **Physical examination:** restricted movements of the back, typical upright positions at later stages, and respiratory abnormalities
- **Laboratory tests:** erythrocyte sedimentation rate (ESR), CRP, rheumatoid factor, immunoglobulin A, and alkaline phosphatase (in severe forms of the disease) levels
- **Test for genetic susceptibility:** human leukocyte antigen B27 (HLA-B27) is detected in 80 to 90% of patients
- **X-ray and/or magnetic resonance imaging (MRI)**
- **Treatment test with nonsteroidal anti-inflammatory drugs (NSAIDs)**

In routine clinical practice, mNY and ASAS classification criteria may be used to support the diagnosis of axSpA depending on the clinical expertise and experience of the treating physician. Classification criteria supporting early diagnosis of axSpA (before patients develop chronic structural damage) were only recently developed; therefore, the most frequently investigated subset of axSpA is AS, and experience with the use of these criteria is still limited.

First line therapy for axSpA consists of NSAIDs and nonpharmacologic treatment, such as patient education and regular exercise/physiotherapy (Braun et al, 2011b). Nonsteroidal anti-inflammatory drugs are effective against the major symptoms of axSpA (pain and stiffness) and there is some evidence that NSAIDs may have disease-modifying properties including retarding the progression of structural spinal damage (Poddubny, 2013; Poddubny et al, 2012b). However, the ability of NSAIDs to modify progression of disease is by no means proven (Haroon et al, 2013).

Conventional disease-modifying antirheumatic drugs (DMARDs; eg, methotrexate and sulfasalazine) are recommended only in patients with predominantly peripheral manifestation (Braun et al, 2011b).

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 (TNF) inhibitors, ie, certolizumab pegol (CZP), adalimumab, etanercept, infliximab, and golimumab, are currently the only effective and approved treatment options. Etanercept, infliximab, and golimumab are indicated for active AS only, while CZP and adalimumab are indicated in both AS and nr-axSpA in some regions.
Certolizumab pegol is a humanized univalent antibody Fab’ fragment conjugated to polyethyleneglycol against human TNFα. Certolizumab pegol has demonstrated efficacy in clinical studies of Crohn’s disease, psoriasis, psoriatic arthritis, rheumatoid arthritis, and axSpA.

The efficacy and safety of CZP have been assessed in a multicenter, randomized, double-blind, placebo-controlled study (AS001, Rapid axSpA; Landewé et al, 2014) in subjects with adult-onset active axSpA (nr-axSpA or AS) for at least 3 months. Subjects were treated with a loading dose of CZP (400mg at Weeks 0, 2 and 4 for both treatment arms) or placebo followed by either 200mg of CZP every 2 weeks or 400mg of CZP every 4 weeks or placebo. The primary efficacy endpoint was the ASAS 20% response criteria (ASAS20) at Week 12.

AS001 demonstrated clinical efficacy in subjects treated with CZP on multiple measures of signs and symptoms of axSpA. Improvements in measures of inflammation on imaging and in blood samples, physical function, pain, fatigue, productivity outside and within the home, and health-related quality of life were also attained. There were clinically meaningful improvements in both treatment groups compared with placebo in the overall axSpA population as well as the AS and nr-axSpA subpopulations with no clinically relevant differences between the 2 dosing regimens. The safety profile of CZP in subjects with active axSpA was consistent with that expected in subjects with inflammatory joint diseases receiving an anti-TNF agent and with previous studies of CZP.

Based on the results of AS001, CZP (Cimzia®) was approved in the EU and several other countries, eg, Turkey, Argentina, and Chile, for the treatment of adult patients with severe active axSpA (comprising AS and nr-axSpA); and was approved for the treatment of adults with active AS in the USA, Canada, and Australia.

In Europe, CZP is indicated for the treatment of rheumatoid arthritis, psoriatic arthritis, and severe active axSpA, comprising:

- Ankylosing spondylitis (AS): adults with severe active AS who have had an inadequate response to, or are intolerant to NSAIDs
- Axial spondyloarthritis without radiographic evidence of AS: adults with severe active axSpA without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to NSAIDs

The launch and reimbursement of CZP in the treatment of axSpA are expected in European countries with different timings.

Data on the efficacy and safety of CZP have been collected only from clinical study populations. To date, information on treatment with CZP in routine clinical practice is not available. This noninterventional study (NIS), the first NIS with CZP in axSpA patients, is designed to assess the effectiveness of CZP in routine clinical practice when the product is administered in accordance with the instructions for use in patients with axSpA. Patients will be followed according to current diagnostic procedures and treatment in their country. The decision for initiating CZP will be independent of study participation, and CZP will be prescribed as per label.
2 STUDY TYPE

This is a European prospective noninterventional cohort study in patients with axSpA (including both AS and nr-axSpA) being treated with CZP. The overall duration of observation per patient will be 12 months (52 weeks).

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this NIS is to assess the effectiveness of CZP in patients with axSpA (AS and nr-axSpA) under routine clinical practice in Europe.

3.2 Secondary objectives

The secondary objectives are:

- To assess the effectiveness of CZP in AS and nr-axSpA subpopulations
- To gain information on peripheral and extra-articular manifestations
- To gain insights on the use of antirheumatic concomitant medications such as synthetic DMARDs and NSAIDs

4 STUDY VARIABLES

In this NIS, assessments will be performed and data collected at Week 0 (Baseline), and approximately Week 12 (Week 6 through 16), Week 24 (Week 17 through 40), and Week 52 (Week 41 through 64).

The effectiveness of CZP will be assessed with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Physician’s Global Assessment of Disease Activity (PhGADA), ASAS20 and ASAS 40% response criteria (ASAS40), Ankylosing Spondylitis Disease Activity Score (ASDAS), and their individual components (see Section 10). The primary measure of the effectiveness of CZP will be the BASDAI; other measures of effectiveness will be considered as secondary and other variables.

4.1 Primary variable

- Change from Baseline in BASDAI to Week 52 in the overall axSpA population, and the AS and nr-axSpA subpopulations

4.2 Secondary variables

The following secondary variables will be assessed in the overall axSpA population, and the AS and nr-axSpA subpopulations:

- Change from Baseline in BASDAI to Weeks 12 and 24
- ASAS20 response criteria at Weeks 12, 24, and 52
- ASAS40 response criteria at Weeks 12, 24, and 52
- Change from Baseline in BASFI to Weeks 12, 24, and 52
- Change from Baseline in Patient’s Global Assessment of Disease Activity (PtGADA) to Weeks 12, 24, and 52
4.3 Other variables

The following other variables will be assessed in the overall axSpA population, and the AS and nr-axSpA subpopulations:

- Change from Baseline in CRP level to Weeks 12, 24, and 52
- Change from Baseline in ESR to Weeks 12, 24, and 52
- Change from Baseline in ASDAS to Weeks 12, 24, and 52
- Change from Baseline in total back pain to Weeks 12, 24, and 52
- Change from Baseline in the concomitant intake of synthetic DMARDs to Weeks 12, 24, and 52
- Change from Baseline in the concomitant intake of NSAIDs to Weeks 12, 24, and 52
- Presence of peripheral manifestations at Baseline, Weeks 12, 24, and 52
- Presence of extra-articular manifestations at Baseline, Weeks 12, 24, and 52
- Change from Baseline in PhGADA to Weeks 12, 24, and 52

4.4 Safety variable

All adverse drug reactions (ADRs) will be collected and summarized.

5 STUDY DESIGN

This is a European multicenter, prospective noninterventional cohort study in axSpA patients who have been newly prescribed CZP. A total of 678 patients with axSpA, approximately 488 with AS and 190 with nr-axSpA, will be followed in this study. Sample size rationale is discussed in Section 12.4. Patients will be followed for approximately 52 weeks.

The choice of medical treatment with CZP is made independently by the treating physician in the regular course of practice and is not influenced by the NIS observational plan. The decision to prescribe CZP for a patient with axSpA is based on the physician’s individual clinical diagnosis, disease status, and treatment choice. The physician will not be asked to perform any additional examinations or investigations such as x-ray or MRI. The physician should follow the routine clinical practice for axSpA existing in his/her site/country.

Certolizumab pegol or any other medications will not be provided nor paid for by the Sponsor.

There will be 4 data collection/assessments points (visits): at Week 0 (Baseline), and approximately Week 12 (Week 6 through 16), Week 24 (Week 17 through 40), and Week 52 (Week 41 through 64). None of these visits are required as part of this NIS observational plan; all visits will be scheduled and conducted according to routine clinical practice. An overview of the study flow and assessments is provided in Table 5–1.

Before any data (including information on the initial clinical diagnosis of axSpA) are transferred from the existing medical records to the electronic Documentation form (eDF), a Patient Data Consent form (PDCF) will be signed and dated by the patient.
Data related to the assessment of the actual disease activity/inflammation activity (such as BASDAI, BASFI, PhGADA, and PtGADA) will be assessed and recorded in the patient’s medical records before the first injection of CZP at Visit 1 (Baseline Visit).

**Table 5–1: Overview of study flow and observational assessments**

<table>
<thead>
<tr>
<th>Assessments</th>
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<td>Initial diagnosis</td>
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<td>History of SpA-related manifestations</td>
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<td>BASDAI</td>
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<tr>
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<tr>
<td>Total back pain</td>
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<tr>
<td>CRP level and ESR(^d)</td>
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<td>Peripheral and extra-articular manifestations</td>
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</tr>
<tr>
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<tr>
<td>PhGADA</td>
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</tr>
<tr>
<td>Concomitant medications (antirheumatic drugs)(^e)</td>
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</tr>
<tr>
<td>Withdrawal criteria</td>
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</tr>
<tr>
<td>Hospitalization/emergency room visits</td>
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<tr>
<td>Drug administration (CZP dose and schedule)</td>
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<tr>
<td>Collection of ADRs</td>
<td>X X X</td>
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</table>

ADR=adverse drug reaction; approx.=approximately; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; CRP=C-reactive protein; CZP=certolizumab pegol; ESR=erythrocyte sedimentation rate; PDCF=Patient Data Consent form; PhGADA=Physician’s Global Assessment of Disease Activity; PtGADA=Patient’s Global Assessment of Disease Activity; SpA=spondyloarthritis

\(^a\) All assessments are done only if they reflect the routine clinical practice and do not include any additional diagnostic or therapeutic measures.

\(^b\) Visit schedule should reflect the routine clinical practice; no visits are required as part of the observational plan.

\(^c\) Must be signed prior to Visit 2.
C-reactive protein is preferred, but ESR can be used in case CRP data are not available. For all visits, a constant collection of either CRP or ESR values is preferred for each patient.

Information on concomitant medications will be collected during the observation period (ie, 52 weeks) for all patients regardless of CZP treatment.

6 EXPECTED STUDY DURATION
The expected enrollment period is 18 to 24 months. The overall duration of observation per patient will be 12 months. The observation of the first patient will start following Ethics Committee approval and the patient signing the PDCF. The documentation period for each patient will end with Visit 4 (approximately Week 52).

7 ANTICIPATED REGIONS AND COUNTRIES
This NIS will be conducted in European countries at approximately 100 sites. The study will be initiated in Germany and then extended to other European countries according to reimbursement status of CZP in axSpA indication.

8 SELECTION AND WITHDRAWAL OF PATIENTS
8.1 Selection criteria
The following selection criteria must be followed for patients entering the NIS:

1. The patient personally signed and dated a PDCF prior to Visit 2. No data can be entered into the eDF prior to signature of the PDCF.

2. The patient must have a clinical diagnosis of active axSpA (AS or nr-axSpA) according to the diagnostic criteria used by the physician in routine clinical practice.

3. The decision to prescribe CZP is made by the physician independent of the patient’s participation in the NIS.

4. The patient must be newly prescribed CZP according to local regulations or guidelines (eg, BASDAI≥4).

5. Treatment is according to instructions in the Summary of Product Characteristics (SmPC) for patients considered by the treating physician to be reliable and capable of adhering to the observational plan (eg, able to understand and complete questionnaires).

6. If a patient is participating in an ongoing investigational study, then he/she will not be able to take part in this study.

8.2 Withdrawal criteria
Patients are free to withdraw from the study at any time, without prejudice to their continued care. In the case of withdrawal or discontinuation, the physician should attempt to obtain relevant withdrawal information from the patient. The primary reason for withdrawal or discontinuation (eg, disease remission, consent withdrawn, adverse event (AE), lack/loss of efficacy, lost to follow up) must be documented in the eDF. Refer to Section 11.2 for definitions of lack of efficacy and loss of efficacy.
9 STUDY TREATMENT

The decision to prescribe CZP is made by the treating physician independent of the decision to include the patient in the study. The dose and administration schedule will be according to the current SmPC.

Certolizumab pegol or any other medications will not be provided nor paid for by the Sponsor.

Each patient will receive a 5-digit number assigned when entering the study. The number will serve as the patient’s unique identifier throughout the study.

10 ASSESSMENT OF EFFECTIVENESS

10.1 BASDAI

The most common instrument used to measure the disease activity of AS from the patient’s perspective is the BASDAI (Garrett et al, 1994). The BASDAI is a validated self-reported instrument, which consists of six 10 unit horizontal NRSs to measure severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration) over the last week. The final BASDAI score ranges from 0 to 10, with lower scores indicating lower disease activity.

The BASDAI is calculated as follows:

\[
BASDAI = \frac{Q1 + Q2 + Q3 + Q4 + \frac{Q5 + Q6}{2}}{5}
\]

Fatigue item of the BASDAI

Fatigue can effectively be measured with single-item questions such as the BASDAI item (van Tubergen et al, 2002a). This item has shown moderate to good reliability and responsiveness.

The BASDAI will be completed at Week 0 (Baseline) and Weeks 12, 24, and 52.

10.2 Total back pain

Total pain in the spine experienced by axSpA patients is adequately measured by the following question: “How much pain of your spine do you have due to spondyloarthritis?” using a Numeric Rating Scale (NRS) where 0 is “no pain” and 10 is “worst possible pain” (Sieper et al, 2009; van der Heijde et al, 2005; Haibel et al, 2008).

Total back pain will be measured at Week 0 (Baseline) and Weeks 12, 24, and 52.

10.3 ASAS20 and 40 response

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 domains:

- PtGADA
- Pain assessment (total spinal pain NRS scores)
- Function (represented by BASFI)
- Inflammation (mean of BASDAI questions [Q] 5 and 6 concerning morning stiffness intensity and duration)
and absence of deterioration in the potential remaining domain (deterioration is defined as a relative worsening of at least 20% and an absolute worsening of at least 1 unit).

The ASAS criteria for 40% improvement are defined as relative improvement 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 ASAS20 and 40 will be calculated at Week 0 (Baseline) and Weeks 12, 24, and 52.

10.4 BASFI

The BASFI is a validated disease-specific instrument for assessing physical function (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, 2002b). The BASFI is the mean of the 10 scores such that the total score ranges from 0 to 10, with lower scores indicating better physical function.

The BASFI will be completed at Week 0 (Baseline) and Weeks 12, 24, and 52.

10.5 PhGADA

The physician will assess the overall status of the patient with respect to the axSpA signs and symptoms and the functional capacity of the patient using a NRS where 0 is “very good, asymptomatic and no limitation of normal activities” and 10 is “very poor, very severe symptoms which are intolerable and inability to carry out all normal activities.”

This assessment by the physician should be made blind to the PtGADA.

The PhGADA will be completed at Week 0 (Baseline) and Weeks 12, 24, and 52.

10.6 PtGADA

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.”

The PtGADA will be completed at Week 0 (Baseline) and Weeks 12, 24, and 52.

10.7 ASDAS

The ASDAS is comprised of a number of assessments which are scored by the subject and is calculated as follows (van der Heijde et al, 2009):

- $0.121 \times$ total back pain (BASDAI Q2 result)
- $0.058 \times$ duration of morning stiffness (BASDAI Q6 result)
- $0.110 \times$ PtGADA
- $0.073 \times$ peripheral pain/swelling (BASDAI Q3 result)
- $0.579 \times$ (natural logarithm of the CRP [mg/L]+1)

Total back pain, PtGADA, duration of morning stiffness, peripheral pain/swelling, and fatigue are all assessed on a NRS (0 to 10 units) (Lukas et al, 2009).
The sum of these weighted components gives the ASDAS.

ASDAS(CRP) is preferred, but ASDAS(ESR) can be used in case CRP data are not available.

ASDAS(ESR) is the sum of (Sieper et al, 2009):

- 0.0796 x total back pain (BASDAI Q2 result)
- 0.0696 x duration of morning stiffness (BASDAI Q6 result)
- 0.1136 x PtGADA
- 0.0866 x peripheral pain/swelling (BASDAI Q3 result)
- 0.293 x √ESR

The ASDAS will be calculated at Week 0 (Baseline) and Weeks 12, 24, and 52.

With respect to the evaluation of ASDAS response over time, the treating physician is encouraged to use the same measurement either CRP (which is preferred) or ESR for each patient.

11 SAFETY REPORTING

11.1 Definition of AEs and ADRs

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

An ADR is a response to a medicinal product which is noxious and not intended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. This includes ADRs which arise from:

- The use of a medicinal product within the terms of the marketing authorization
- The use outside the terms of the marketing authorization, including overdose, off-label use, misuse, abuse, and medication errors
- Occupational exposure (this refers to the exposure to a medicinal product as a result of one’s professional or nonprofessional occupation)

11.2 Reporting and description of ADRs

In order to ensure complete safety data collection, all ADRs occurring during the study, including a safety follow-up period of 10 weeks after the last dose of CZP, will be collected. This includes all diseases or conditions that were not present prior to the initial visit and all underlying or previous concomitant diseases that recurred or worsened after the Baseline Visit.

Signs or symptoms of axSpA should be recorded as ADRs 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 treating physician from the patient’s history or the Baseline Visit. New diagnoses or clinically significant worsening of peripheral manifestations
such as peripheral arthritis, enthesitis and dactylitis, or extra-articular manifestations such as uveitis, inflammatory bowel disease (eg, Crohn’s disease/colitis ulcerosa), psoriasis skin lesions, and osteoporosis should be reported as ADRs.

In addition, lack of efficacy, loss of efficacy, and overdosing will also be reported as ADRs. The following definitions should be used:

- **Lack of efficacy**: It is an inappropriate clinical response within 3 months after initialization of a new CZP treatment.
- **Loss of efficacy**: It is the worsening of the clinical condition after a patient initially responded/improved to CZP.
- **Overdose** is defined in Section 11.5. The reaction may be symptomatic, in that the excessive dosing resulting in clinical signs and symptoms, or the excessive intake may itself be the symptom.

When recording an ADR, the treating physician should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The AE Report form and source documents should be consistent.

### 11.3 Follow up on ADRs

An ADR should be followed until it has resolved, has a stable sequelae, the treating physician determines that it is no longer clinically significant, or the patient is lost to follow up.

If an ADR is still ongoing at the end of the study for a patient, follow up should be provided until resolution/stable level of sequelae, the treating physician no longer deems that it is clinically significant, or until the patient is lost to follow up. If no follow up is provided, the treating physician must provide a justification.

### 11.4 Pregnancy

Enrolling physicians are required to report pregnancy and breastfeeding of study participants and pregnancy of study participant partners.

The pregnancy and the outcome (birth, miscarriage, and abortion) will be documented on the Pregnancy Report and Outcome form provided to the treating physician. 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 treating physician has to report on the health of the mother and child. Every reasonable attempt should be made to follow the development and health of the child for at least 30 days after birth for any significant medical issues or development delay.

In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days.

In cases where the partner of a male patient enrolled in the NIS becomes pregnant and especially in case of suspected exposure via semen, UCB will ask the treating physician or designee to contact the patient and his partner to request consent via the Partner Pregnancy Consent form to contact the pregnant woman’s treating physician. If she agrees to provide additional information, the Pregnancy Report and Outcome form will be forwarded to the patient’s partner for completion.
11.5 Overdose of observed medications

Excessive dosing (beyond what is in the approved SmPC) should be reported on the AE Report form, and considered as an ADR, whether the overdose is associated with an ADR or not. Any event associated with excessive dosing must be reported and followed as an ADR.

11.6 Safety signal detection

Reported ADRs from this study will be reviewed periodically together with other safety information received at UCB, to detect as early as possible any safety concern(s) related to the treatment so that treating physicians, patients, and regulatory authorities will be informed appropriately, and as early as possible.

11.7 Procedures for reporting ADRs

The patient will be given the opportunity to report ADRs. A general prompt will also be given at each study visit to report ADRs, for example: “Did you notice anything unusual about your health (since your last visit)?”

In addition, the treating physician should review any self-assessment procedures (eg, questionnaires) employed.

Adverse drug reactions must be reported on the provided AE Report form for NIS. If an ADR is reported, UCB must be informed within 1 working day of receipt of this information by the site (see Drug Safety [DS] contact information). The treating physician must forward to UCB’s local DS department a duly completed AE Report form for NIS 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.

If clarifications on an ADR are necessary, UCB’s local DS department shall request additional information from the treating physician. He/she shall provide the requested information within a timely manner (maximum 7 calendar days) to allow accurate and timely reporting to the concerned regulatory authorities, if applicable.

As much as possible, the AE Report form for NIS and other requested information should be provided in English.

Additional information (eg, autopsy or laboratory reports) received by the treating physician must be provided within 1 working day. 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 AE Report form for NIS. Translations into English language will be done by UCB’s local DS department.

11.8 AEs of interest

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

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

In addition to AEs of interest, incidences of injection site pain and injection site reaction should be collected as ADRs.

12 STATISTICS

A description of statistical methods is presented below and will be described in more detail in the Statistical Analysis Plan (SAP). Statistical analysis and generation of tables, figures, and listings will be performed using SAS® Version 9.1.3 or higher. All statistical analyses will be descriptive and explorative in nature. No inferential statistical analyses are planned for the analysis of the study variables. All analyses will be tabulated using observed and imputed data, if applicable.

12.1 Definition of analysis sets

For this study, the following definitions will apply:

The Safety Set (SS) will consist of all subjects who have received at least 1 dose of CZP and will be used to assess safety variables.

The Full Analysis Set (FAS) will consist of all subjects in the SS who have received at least 1 dose of CZP, have a valid Baseline, and have at least 1 valid post-Baseline measurement for the BASDAI. The FAS will be used to assess variables describing effectiveness.

12.2 Planned analyses

12.2.1 Analysis of the primary variable

The primary variable will be the change from Baseline in BASDAI to Week 52 in the overall axSpA population, and the AS and nr-axSpA subpopulations.

The change from Baseline in BASDAI will be analyzed using descriptive statistics for the overall axSpA population, and the AS and nr-axSpA subpopulations.

12.2.2 Analysis of secondary variables and other variables

Descriptive statistics will be used for quantitative and binary variables at the first visit and each scheduled visit.

Summary statistics for continuous variables will include: number of available observations, mean, standard deviation (SD), minimum, median, maximum for each subgroup and overall. Number, percentage, and 95% two-sided confidence intervals (CI) will be presented for binary variables.
12.2.3 Analysis of safety variables

Adverse drug reactions will be coded for analysis according to the Medical Dictionary for Regulatory Activities (MedDRA®).

Adverse drug reactions that occur during this study will be presented by system organ class and preferred term in a frequency table giving the number of events, the number of patients, and the percentage of patients who experience the event by subpopulation.

12.2.4 Other analyses

Prior and concomitant medications as well as medical history will be summarized using frequency tables. Demographic variables will be summarized using descriptive statistics. The follow-up axSpA treatment of patients who permanently discontinue CZP will be summarized using frequency tables.

12.2.5 Subgroup analyses

All above stated analyses of primary and secondary variables will be conducted in subgroup analyses with the following subgroups:

- TNF inhibitor naïve patients
- TNF inhibitor pretreated patients

12.2.6 Analysis of missing data

Missing data for the variables describing effectiveness will be imputed using a missing at random approach (eg, mixed model with repeated measures). Model specifications will be provided in the SAP.

If there are individual missing items in questionnaires or missing components in composite variables, their total score will be set to missing unless specified otherwise. Missing or partial dates will be imputed.

Details on missing data handling will be provided in the SAP.

12.3 Planned interim analysis and data monitoring

At least 1 interim analysis is planned. No data monitoring is planned.

12.4 Determination of sample size

Based on the literature (Poddubnyy et al, 2011; Poddubnyy et al, 2012a; Braun et al, 2011a), it is assumed that 28% (may vary between 21 and 44%) of patients in a referred patient population with a diagnosis of axSpA have nr-axSpA.

In the Rapid axSpA study, the mean change from Baseline in the BASDAI at Week 48 in subjects treated with CZP was -3.26 with a SD of 2.17, corresponding to a coefficient of variation (CV) of approximately 66.6%. For the AS and nr-axSpA subpopulations, the mean change from Baseline was -3.17 (SD=2.16), and -3.36 (SD=2.19), respectively.

For the sample size calculation, we assume slightly more conservative mean change from Baseline in the BASDAI of 3.0 with a SD of 2.25, corresponding to a slightly increased CV of 75%.
For obtaining a maximum extension of the 2-sided 95% CI of 0.358 for the change from Baseline in BASDAI in patients with nr-axSpA, 152 patients need to be included in the study. Given the assumptions above, the 95% CI would extent to less than 12% from the mean change from Baseline. Based on the diagnosis distribution above, 390 patients with AS would lead to a maximum extension of the 95% CI of 0.223 (ie, less than 7.5% extension from the mean change from Baseline). The resulting total number of axSpA patients would be 542 leading to a maximum extension of the 95% CI of 0.189 (ie, an extension of 6.3% from the mean change from Baseline).

It is assumed that 20% of the included patients in both indications will either not deliver usable information for the 12-week assessments or may not be classified in the 2 indications correctly, therefore the sample size will be $\frac{542}{0.8}=678$ (ie, $\frac{152}{0.8}+\frac{390}{0.8}=190+488=678$).

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 Quality assurance

13.1.1 Monitoring

In order to safeguard and assure data quality, a site management plan will be developed that will include details on site monitoring visits, site management by telephone, and source data verification.

Training on study procedures (eg, the handling of the eDF and the reporting of ADRs, or AEs of interest) will be provided during site initiation. Any medical and/or methodological questions arising during the study will be answered by UCB or designee.

13.1.2 Data management

13.1.2.1 eDF completion

The study is performed using electronic data capture. The treating physician is responsible for prompt reporting of accurate and complete data in the eDFs and in all required reports. Any change or correction to the eDF after saving must be accompanied by a reason for the change. Corrections made after the treating physician’s review and approval (by means of a password/electronic signature) will be reapproved by the treating physician. The treating physician should maintain a list of personnel authorized to enter data into the eDF. Detailed instructions will be provided in the eDF Completion Guidelines.

13.1.2.2 Database entry and reconciliation

Electronic documentation forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data are entered into the eDFs once and are subsequently verified. An electronic audit trail system will be maintained within the clinical data management system to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.
13.1.2.3 Coding dictionaries
Medications will be coded with the World Health Organization Drug Dictionary and ADRs will be coded according to MedDRA®. In both cases, the version used will be that current to the Sponsor at the time of data capture.

13.2 Termination of study
As soon as the planned number of 678 patients has been enrolled, no additional patients will be enrolled in the study.

For the individual patient, this NIS will end with the documentation conducted during their final visit. Study participation can also be terminated by the patient at any time.

The Sponsor reserves the right to terminate the study at an early stage and/or to close individual sites. Potential reasons for an early termination include:

- An insufficient number of patients included into the study
- Upon the request of regulatory authorities
- The participating physician does not adhere to the applicable rules, provisions, laws, and guidelines

Patients who discontinue from CZP will be followed until Week 52.

13.3 Data archiving
Immediately after approval of the final report, the documentation forms will be archived for a minimum period of 10 years, including the ADR documentation and ADR correspondence. The latter will be archived by the UCB DS department without any time constraints.

13.4 Legal provisions and ethics
13.4.1 Data protection and data privacy declaration
The legal provisions for data protection will be observed. Prior to inclusion, the patient will be given information in writing that describes the purpose and procedures of the study and explains the requirements of data protection. The patient has to agree in writing that his/her medical data will be used for the evaluation of the study results by signing a study-specific PDCF.

Information relating to participating physicians will be declared, and the physicians will be informed, within the framework of their financial agreement, of their right to access, object to, and correct this information.

13.4.2 Report of the Ethics Committee
Prior to the implementation of this NIS, a positive vote will be obtained from the appropriate national scientific and ethical bodies in accordance with any local regulations and laws.

13.4.3 Legally required reports
This NIS is not interventional, because it only pursues the objective of documenting the standard practical procedures and/or the data associated with the treatment of patients suffering from axSpA.
The study will be entered into the official online registry of clinical studies that is maintained by the US National Institutes of Health (http://www.clinicaltrials.gov) and is accessible to the public at large.

14 REMUNERATION

Any payments to physicians will be in accordance with any local regulations and laws and will compensate only the additional work load related to the conduct of the study. The remuneration shall be regulated in a separate agreement to be concluded between UCB Biopharma SPRL and the participating physician and/or his/her clinic administration.

15 FINAL REPORT AND PUBLICATION

Interim analysis report and final report will be submitted as appropriate. In addition, a revision report will be provided as applicable to the reporting country.

16 REFERENCES


17 APPENDICES

17.1 NIS Observational Plan Amendment 1

Rationale for the amendment

The observational plan has been updated to account for administrative and standard of practice changes at the clinical sites.

Additionally, to ensure recording of well classified ADRs and to avoid unnecessary reporting internally and to the authorities, the text has been clarified to state that ADRs (serious and nonserious) need to be collected. In addition, it has been clarified that lack of efficacy, loss of efficacy, and overdose, should be reported as ADRs.

Provision for at least 1 interim analysis has been added, to allow interim review of data in this long duration study and to fulfill local reporting requirements.

Several selection criteria were clarified to aid selection of an appropriate patient population.

Modifications and changes

Global changes

The following changes were made throughout the observational plan:

• Administrative and standard of practice changes at the clinical sites
• Lack of efficacy, loss of efficacy, and overdose to be reported as ADRs
• Interim analysis and reporting to be done
• Selection criteria modified

Specific changes

Specific changes made in the observational plan are as follows:
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<th>Section</th>
<th>Previous text</th>
<th>Amended text</th>
<th>Reason for change</th>
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<td>Final Noninterventional Study Observational Plan 17 Jul 2014 Noninterventional Study Observational Plan Amendment 1 15 Dec 2015</td>
<td>Administrative update</td>
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<td>STUDY CONTACT INFORMATION</td>
<td>Sponsor Study Physician Name: [Redacted] Address: UCB Pharma GmbH Alfred Nobel Straße 10 40789 Monheim am Rhein GERMANY SPRL Allée de la Recherche 60 B-1070 Brussels BELGIUM</td>
<td>Sponsor Study Physician [Redacted] 190 Rue Championnet 75018, Paris FRANCE SPRL Alfred Nobel Straße 10 40789 Monheim am Rhein GERMANY</td>
<td>Administrative update</td>
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### Table 17–1: Amendment 1 specific changes

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<td>STUDY CONTACT INFORMATION</td>
<td>Contact for Adverse Drug Reaction Reports (24h), Adverse Events of Interest (24h), Safety Relevant Reports, and Pregnancy Reports Fax: Germany: +49 2173 48 2010 Austria: +43 1291 80 21 Netherlands: +31 76 587 5264 Sweden: +45 32 46 24 01 Greece: +30 210 9974199 United Kingdom: +44 1 753 447 858 Email: Germany: <a href="mailto:ds.de@ucb.com">ds.de@ucb.com</a> Austria: <a href="mailto:ds.at@ucb.com">ds.at@ucb.com</a> Netherlands: <a href="mailto:ds.nl@ucb.com">ds.nl@ucb.com</a> Sweden: <a href="mailto:ds.se-dk@ucb.com">ds.se-dk@ucb.com</a> Greece: <a href="mailto:ds.gr@ucb.com">ds.gr@ucb.com</a> United Kingdom: <a href="mailto:ds.uk@ucb.com">ds.uk@ucb.com</a></td>
<td>Contact for Adverse Drug Reaction Reports (24h), Adverse Events of Interest (24h), Safety Relevant Reports, and Pregnancy Reports Fax: Germany: +49 2173 48 2010 Spain: +34 91 57 22572 Italy: +39 02 30079 246 Belgium: +32 2 559 9009 Greece: +30 210 9974199 United Kingdom: +44 1 753 447 858 Email: Germany: <a href="mailto:ds.de@ucb.com">ds.de@ucb.com</a> Spain: <a href="mailto:drugsafetyspain@ucb.com">drugsafetyspain@ucb.com</a> Italy: <a href="mailto:ds.it@ucb.com">ds.it@ucb.com</a> Belgium: <a href="mailto:ds.be@ucb.com">ds.be@ucb.com</a> Greece: <a href="mailto:ds.gr@ucb.com">ds.gr@ucb.com</a> United Kingdom: <a href="mailto:ds.uk@ucb.com">ds.uk@ucb.com</a></td>
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<td>4</td>
<td>DECLARATIONS AND SIGNATURES</td>
<td>Declarations and signatures of persons responsible for the study confirm that I have carefully read and understood this NIS observational plan and agree to conduct this NIS observational plan as outlined.</td>
<td>(This section has been moved to the last section.) Declarations and signatures of persons responsible for the study confirm that I have carefully read and understand this NIS observational plan and agree to conduct this NIS as outlined in this observational plan.</td>
<td>Administrative update</td>
</tr>
<tr>
<td>5</td>
<td>Declaration and signature of Physician</td>
<td>I confirm that I have carefully read and understood this NIS observational plan and agree to conduct this study as outlined in this NIS observational plan and local laws and requirements.</td>
<td>(This section has been moved to the last section.) I confirm that I have carefully read and understood this NIS observational plan and agree to conduct this study as outlined in this NIS observational plan and local laws and requirements.</td>
<td>Administrative update</td>
</tr>
</tbody>
</table>
Table 17-1: Amendment 1 specific changes

<table>
<thead>
<tr>
<th>Change number</th>
<th>Section</th>
<th>Previous text</th>
<th>Amended text</th>
<th>Reason for change</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Section 4.4, Safety variable</td>
<td>Adverse drug reactions (ADRs) will be collected and summarized.</td>
<td>All adverse drug reactions (ADRs) will be collected and summarized.</td>
<td>The changes are made to avoid unnecessary reporting internally and to the authorities.</td>
</tr>
<tr>
<td>7</td>
<td>Section 5, STUDY DESIGN</td>
<td>Table 5-1: Row: Recording of ADRs</td>
<td>Table 5-1: Row: Collection of ADRs</td>
<td>The changes made accommodate updates to the style requirements, changes in standard practice at clinical sites, and also for the purpose of clarity.</td>
</tr>
</tbody>
</table>
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</tr>
</thead>
</table>
| 8             | Section 8.1, Selection criteria | 1. The patient personally signed and dated a PDCF at Visit 1.  
4. The patient must be newly prescribed CZP. | 1. The patient personally signed and dated a PDCF prior to Visit 2.  
4. The patient must be newly prescribed CZP according to local regulations or guidelines (eg, BASDAI≥4).  
6. If a patient is participating in an ongoing investigational study, then he/she will not be able to take part in this study. | Change in standard of practice at clinical sites  
Also additional details provided for clarity                                                                 |
| 9             | Section 8.2, Withdrawal criteria | The primary reason for withdrawal or discontinuation must be documented in the eDF. | The primary reason for withdrawal or discontinuation (eg, disease remission, consent withdrawn, adverse event (AE), lack/loss of efficacy, lost to follow up) must be documented in the eDF. Refer to Section 11.2 for definitions of lack of efficacy and loss of efficacy. | Details added to aid clarity                                                                 |
| 10            | Section 10.7, ASDAS          | None                                                                         | With respect to the evaluation of ASDAS response over time, the treating physician is encouraged to use the same measurement either CRP (which is preferred) or ESR for each patient. | Details added to aid clarity                                                                 |

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## Table 17–1: Amendment 1 specific changes

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<tbody>
<tr>
<td>11</td>
<td>Section 11.1, Definition of AEs and ADRs</td>
<td>An ADR is a response to a medicinal product which is noxious and not intended.</td>
<td>An ADR is a response to a medicinal product which is noxious and not intended. <strong>Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.</strong></td>
<td>Definition provided for clarity purpose</td>
</tr>
<tr>
<td>12</td>
<td>Section 11.2, Reporting and description of ADRs</td>
<td>In order to ensure complete safety data collection, all ADRs occurring during the study (ie, after signing the PDCF), including a safety follow-up period of 10 weeks after the last dose of CZP, must be reported.</td>
<td>In order to ensure complete safety data collection, all ADRs occurring during the study, including a safety follow-up period of 10 weeks after the last dose of CZP, <strong>will be collected.</strong></td>
<td>For clarity purpose</td>
</tr>
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</table>
| 13            | Section 11.2, Reporting and description of ADRs | None | In addition, lack of efficacy, loss of efficacy, and overdosing will also be reported as ADRs. The following definitions should be used:  
- Lack of efficacy: It is an inappropriate clinical response within 3 months after initialization of a new CZP treatment.  
- Loss of efficacy: It is the worsening of the clinical condition after a patient initially responded/improved to CZP.  
- Overdose is defined in Section 11.5. The reaction may be symptomatic, in that the excessive dosing resulting in clinical signs and symptoms, or the excessive intake may itself be the symptom. | For clarity purpose |
| 14            | Section 11.5, Overdose of observed medications | Excessive dosing (beyond what is in the approved SmPC) should be reported on the AE Report form, whether the overdose is associated with an ADR or not. | Excessive dosing (beyond what is in the approved SmPC) should be reported on the AE Report form, and considered as an ADR, whether the overdose is associated with an ADR or not. | For clarity purpose |
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</table>
| 15 | Section 12.2.5, Subgroup analyses | All above stated analyses of primary and secondary variables will be conducted in subgroup analyses with the following subgroups:  
- Anti-TNF naïve patients  
- Anti-TNF pretreated patients | All above stated analyses of primary and secondary variables will be conducted in subgroup analyses with the following subgroups:  
- TNF inhibitor naïve patients  
- TNF inhibitor pretreated patients | For clarity purpose |
| 16 | Section 12.3, Planned interim analysis and data monitoring | No interim analyses or data monitoring are planned. | At least 1 interim analysis is planned. No data monitoring is planned. | To fulfill local reporting requirements |
| 17 | Section 15, FINAL REPORT AND PUBLICATION | A final report will be submitted as appropriate. | Interim analysis report and final report will be submitted as appropriate. In addition, a revision report will be provided as applicable to the reporting country. | To fulfill local reporting requirements |
| 18 | Typographical and style updates were made in the document, but not listed individually in the specific changes list. |
18 DECLARATION AND SIGNATURE OF PHYSICIAN

I confirm that I have carefully read and understood this NIS observational plan and agree to conduct this study as outlined in this NIS observational plan and local laws and requirements.

I will ensure that all physicians and other staff members read and understand all aspects of this NIS observational plan.

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

The objectives and content of this NIS observational plan 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 Biopharma SPRL.

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

Treating physician

<Insert name> _____________________________

Date/Signature
19   SPONSOR DECLARATION

I confirm that I have carefully read and understand this NIS observational plan and agree to conduct this NIS as outlined in this observational plan.
AS0002-Protocol Amendment 1-Noninterventional study (NIS), Multicenter, Cohort

**Electronic Signatures**

<table>
<thead>
<tr>
<th>Signed by</th>
<th>Meaning of Signature</th>
<th>Server Approval Date (dd-mon-yyyy (HH:mm))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical Approval</td>
<td></td>
</tr>
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</table>