PROTOCOL RA0027 AMENDMENT 3

FαsT: TNFα: Observation of Treatment with Certolizumab pegol in Daily Practice

A MULTICENTER, OBSERVATIONAL, NONINTERVENTIONAL STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ANTI-TNF ALPHA THERAPY WITH CERTOLIZUMAB PEGOL OBSERVED IN DAILY PRACTICE IN ADULT RHEUMATOID ARTHRITIS (RA) PATIENTS

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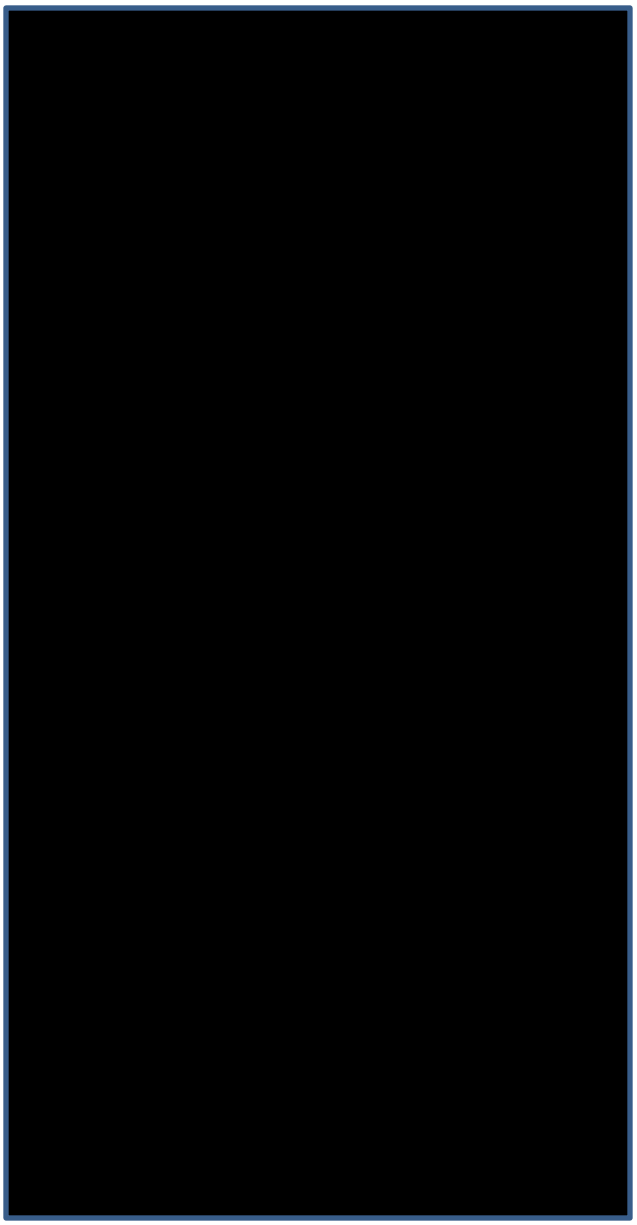
Protocol/Amendment Number	Date	Type of amendment
Final Protocol	06 Jul 2009	N/A
Protocol Amendment 1	12 Oct 2009	Nonsubstantial
Protocol Amendment 2	21 Oct 2010	Nonsubstantial
Protocol Amendment 3	02 May 2012	Substantial

SPONSOR AUTHORIZATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol.



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STUDY CONTACT INFORMATION

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SERIOUS ADVERSE EVENT REPORTING

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LIST OF ABBREVIATIONS

ACPA	anti-cytoplasmatic antibodies
ACR	American College of Rheumatology
AE	adverse event
CDAI	Clinical Disease Activity Index
CDMS	clinical data monitoring system
CI	confidence interval
CRP	c-reactive protein
CRO	contract research organization
CZP	certolizumab pegol
DAS28	28-joint count Disease Activity Score
DMARD	disease modifying antirheumatic drug
EC	ethics committee
EQ-5D	Euro Quality of Life – 5Dimensions
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HAQ-DI	Health Assessment Questionnaire-Disability Index
IP	interphalangeal
IEC	independent ethics committee
IRB	institutional review board
MCP	metacarpophalangeal joints
MCV	mutated citrullinated vimentin
NSAID	nonsteroidal anti-inflammatory drug
PASS	postauthorization safety study
PIP	proximal interphalangeals
PT	preferred term
PtGADA	Patient's Global Assessment of Disease Activity
QoL	quality of life
RA	rheumatoid arthritis
SAE	serious adverse event
SJC	swollen joint count
SmPC	summary of product characteristics
SOC	system organ class
SOP	standard operating procedure

SS	Safety Set
TEAE	treatment emergent adverse event
TJC	tender joint count
TNFα	tumor necrosis factor alpha
VAS	visual analogue scale

1 SUMMARY

This is an observational, noninterventional, noncomparative, postauthorization safety study designed to assess the safety and efficacy of certolizumab pegol (CZP) in long-term use (2 years) in standard daily clinical practice. The observational nature of the study leaves the therapeutic decision exclusively within the discretion of the physician. Procedures and assessments are not to go beyond what is standard in clinical practice. Treatment is only to follow standard medical practice as decided by the physician and as directed in the current Summary of Product Characteristics (SmPC).

The primary objective is to assess the clinical efficacy of CZP in achieving clinical remission after 2 years of therapy in adult patients with rheumatoid arthritis (RA). The secondary objective is to assess the effect of treatment with CZP on patients' arthritis pain, physical function, and the Clinical Disease Activity Index (CDAI) after 2 years of therapy. Other objectives include the assessment of clinical remission, identification of responders to treatment, pharmacoeconomics, change in arthritis pain, fatigue, and physical function per visit, and information on the prescribing habits of physicians with regards to the concomitant treatment.

The primary efficacy variable is clinical remission at Visit 9 (around Week 104) (defined as 28-joint count Disease Activity Score [DAS28 of <2.6]). Other efficacy variables include change from Baseline in patient's arthritis pain, levels of fatigue, health status, and physical functions assessed by the patient, clinical remission by visit, and pharmacoeconomic information.

Management of adverse events (AEs) will be handled according to drug safety regulations in Germany.

A total of 1068 patients across 160 sites in Germany are planned to be observed in this study. It is anticipated that the study will run from Q3 2009 (First Patient First Visit) to Q4 2014 (Last Patient Last Visit). The maximum duration of participation for individual patients will be 116 weeks.

2 INTRODUCTION

This noninterventional, postauthorization safety study is designed to assess the efficacy and safety of CZP in long-term use (2 years) in standard clinical practice according to the instructions for the use in patients with RA as described in the SmPC.

Rheumatoid arthritis is a chronic systemic inflammatory disease that is associated with significant morbidity and mortality. The disease is characterized by inflammation of the synovial lined diarthrodial joints that can result in pain, swelling and joint damage with secondary deformity and progressive disability and impairment of patient health related quality of life (QoL). It is estimated that about 1% of the population worldwide has RA.

Certolizumab pegol is a recombinant, humanized antibody Fab′-fragment that is produced in an *Escherichia coli* expression system. The antibody fragment is subsequently purified and conjugated with high molecular weight polyethylene glycol (40kDA).

Certolizumab pegol has a high affinity for human tumor necrosis factor alpha (TNFα) and binds with a dissociation constant of 90pM. Tumor necrosis factor alpha is a key proinflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralizes TNFα (Inhibitory Concentration at 90% of 4ng/mL for inhibition of human TNFα in the in vitro L929 murine fibrosarcoma cytotoxicity assay) but does not neutralize lymphotoxin α (TNF beta).

Certolizumab pegol was shown to neutralize membrane-associated and soluble human TNFα in a dose-dependent manner. Incubation of monocytes with CZP resulted in a dose-dependent inhibition of lipopolysaccharide-induced TNFα and IL1β production in human monocytes. Certolizumab pegol does not contain a fragment crystallizable region, which is normally present in a complete antibody, and therefore does not fix, complement, or cause antibody-dependent, cell-mediated cytotoxicity in vitro. It does not induce apoptosis in vitro in human peripheral blood-derived monocytes or lymphocytes, or neutrophil degranulation.

Certolizumab pegol is approved in the European Union, Switzerland, the United States, and Canada for the treatment of adults with moderately to severely active RA. Certolizumab pegol can be given as monotherapy or concomitantly with methotrexate or nonbiological DMARDs.

In placebo-controlled trials in adult patients with active RA (see SmPC), CZP has been shown to improve signs and symptoms, physical function, fatigue, health-related QoL, and RA-related productivity (at work and within the home), and inhibit the progression of structural damage.

The formation of antibodies to CZP is associated with lowered drug plasma concentrations and in some patients reduced efficacy. Approximately 7.7% of patients in Phase 3 trials (see SmPC) had antibodies to CZP, of which one third had antibodies with neutralizing activity in vitro. Patients treated with concomitant immunosuppressants had a lower rate of antibody development than patients who had not been taking immunosuppressants at Baseline.

The current study aims to assess efficacy and safety data collected in a real life setting in a defined patient population (age, gender, etc.). Identified and potential risks of CZP treatment can be taken from the current version of the SmPC.

Since the study patients will receive CZP in accordance with the SmPC guidance, the risk for the patients is not considered to be increased as a result of their participation in this noninterventional study.

3 STUDY OBJECTIVES

3.1 Primary objective

The purpose of this study is to assess the clinical efficacy of CZP in achieving clinical remission (DAS28 of <2.6) after 2 years of therapy in adult patients with RA.

3.2 Secondary objectives

The secondary objective is to assess the effect of treatment with CZP on patients' arthritis pain, physical function, and disease activity after 2 years of therapy.

3.3 Other objectives

- Assessment of clinical remission and low disease activity for all patients by visit and for different patient populations, based on DAS28 and American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2011 remission criteria
- Identification of responder/nonresponder to CZP treatment as basis for subgroup classification. A patient is considered to be a responder if the DAS28 decrease is ≥1.2 (see Section 12.3.1)
- Gather information on prescribing habits of the rheumatologists with regards to the concomitant treatment
- Gather information on prescribing habits of rheumatologists with regards to the concomitant RA treatment as well as subsequent treatments in case of CZP discontinuation
- Assess incidence of CZP discontinuation due to remission (DAS28)
- To evaluate and assess the effect of treatment over time with CZP for the following:
  - Arthritis pain (Arthritis pain visual analogue scale [VAS])
  - Fatigue (Fatigue Assessment Scale)
  - Physical function (HAQ-DI) and health related quality of life (EQ-5D)
  - Selected components of the American College of Rheumatology diagnostic and improvement criteria: morning stiffness, tender joint count (TJC), swollen joint count (SJC), C-reactive protein (CRP), or erythrocyte sedimentation rate (ESR)
  - Disease activity (CDAI)
  - Pharmacoeconomic data (missing days at work and employment information)
  - Duration of morning stiffness (in hours)

3.4 Safety objectives

To assess safety data collected in a real life setting in a defined patient population (age, gender, etc.) treated with CZP. Identified and potential risks are specified in the current version of the SmPC.

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variable

Clinical remission at Visit 9 (around Week 104) (defined as DAS28 of <2.6).

4.1.2 Secondary efficacy variables

- Change from Baseline in patient's arthritis pain as measured by Patient's Assessment of Arthritis Pain VAS at Visit 9 (around Week 104)
- Change from Baseline in patient's physical function as measured by the HAQ-DI (by Fries et al, 1980 and Lautenschläger et al,1997) at Visit 9 (around Week 104)
- Change from Baseline in disease activity measured by CDAI at Visit 9 (around Week 104)

4.1.3 Other efficacy variables

- Clinical remission (DAS28 of <2.6) by visit
- Low disease activity (DAS28 of ≤3.2) by visit
- Proportion of patients achieving clinical response to treatment based on DAS28 reduction of ≥1.2 by visit
- Change from Baseline CDAI by visit
- Change in patient's arthritis pain as measured by Patient's Assessment of Arthritis Pain VAS by visit
- Change from Baseline in patient's fatigue as measured by Fatigue Assessment Scale by visit
- Change from Baseline in patient's physical function as measured by the HAQ-DI (Fries et al, 1980 and Lautenschläger et al, 1997) by visit
- Change from Baseline in health-related QoL measured as EQ-5D by visit, using the VAS part of the EQ-5D.
- Change from Baseline in quantity of concomitant DMARDs
- Change from Baseline in quantity of concomitant corticosteroids
- Incidence of discontinuation of CZP treatment due to DAS28 (CRP) remission
- Change from Baseline in duration of morning stiffness (in hours) by visit
- Change from Baseline in number of swollen and tender joints by visit (joint scores –TJC and SJC)
- Proportion of patients in clinical remission as defined by the ACR/EULAR 2011 remission criteria
- Employment status

- Employability due to RA
- Sick leave
- RA treatment following discontinuation of CZP

4.2 Safety variable

- Incidence of AEs

5 STUDY DESIGN

5.1 Study description

This is an observational, noninterventional, noncomparative, postauthorization safety study (PASS) to evaluate efficacy and long-term safety of CZP in adult patients with RA in need of treatment with a biologic.

The purpose of this study is to assess the clinical efficacy of CZP in achieving clinical remission with a DAS28 <2.6 after 2 years of therapy. The long-term safety will be evaluated, using reported treatment emergent adverse events.

The observational nature of the study leaves the therapeutic decision exclusively within the discretion of the treating physician. First the decision to treat the patient with CZP needs to be taken, before the treating physician can enroll the patient into this study. In addition, patient procedures and assessments will be performed in the frame of current standard clinical practice and as directed in the SmPC. Management of AEs will be handled according to drug safety regulations in Germany.

5.1.1 Study duration

The entire study duration per patient is intended to be 116 weeks if not prematurely discontinued (see Section 6.3 for withdrawal criteria).

Intervals of visits:

- Baseline Visit at onset of therapy (after deciding to treat the patient with CZP).
  Note: A patient may be enrolled into the study after the start of CZP treatment if he/she met all inclusion and exclusion criteria at the start of CZP treatment. Written data consent must be obtained no later than the start of Visit 2 and prior to conducting any clinical assessment at Visit 2. Following written data consent (ie, enrollment into the study), all relevant data from original records will be entered onto study-specific forms.
- Frequent visits are expected around Weeks 6, 12, 24, 36, 52, 64, 76, and 104: evaluation of efficacy and safety by the treating physician.
- Safety Follow-Up Visit around Week 116.

Patients who stop CZP for lack of efficacy or safety reasons will be followed up for 84 days to analyze which treatments were commonly used after treatment failure of CZP.

Patients who discontinue CZP treatment due to personal reasons or as a result of the treating physician's decision will also be followed up for 84 days (except for patients who withdraw consent and cannot be followed up further).

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

It is anticipated that this study will be conducted from Q3 2009 to Q4 2014.

5.1.2 Number of planned patients and sites

Physicians treating RA patients with biologics will be invited to participate in this PASS. Appropriate selection of the study sites will ensure collection of data representative for the general RA population.

The study will be conducted at approximately 160 sites in Germany. A total of 1068 patients are planned to be enrolled in this study, after the treating physician has made the decision to treat the patient with CZP.

5.2 Schedule of study assessments

The schedule of study assessments by visit are presented below.

Assessments[a]	**Treatment period[b]**									**Safety Follow-Up**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Week	**0**	**6**	**12**	**24**	**36**	**52**	**64**	**76**	**104**	**116**
Written Data Consent[c]	X	X								
Demographics / Medical History	X									
Presence of Rheumatoid Factor	X									
Presence of anti-cyclic citrullinated peptide antibodies	X									
RA history	X									
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Drug administration	X	X	X	X	X	X	X	X	X	
Joint scores (TJC, SJC) (28 joint count)	X	X	X	X	X	X	X	X	X	
Acute phase reactant (CRP or ESR)	X	X	X	X	X	X	X	X	X	
Morning stiffness	X	X	X	X	X	X	X	X	X	
Patient’s Global Assessment of Disease Activity (VAS)	X	X	X	X	X	X	X	X	X	
Physician’s Global Assessment of Disease Activity (VAS)	X	X	X	X	X	X	X	X	X	

Assessments[a]	Treatment period[b]									Safety Follow-Up
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Week	**0**	**6**	**12**	**24**	**36**	**52**	**64**	**76**	**104**	**116**
Arthritis pain VAS	X	X	X	X	X	X	X	X	X	
Fatigue Assessment Scale	X	X	X	X	X	X	X	X	X	
HAQ-DI	X	X	X	X	X	X	X	X	X	
EQ-5D	X	X	X	X	X	X	X	X	X	
Sick leave	X	X	X	X	X	X	X	X	X	
Employment status and employability due to RA	X	X	X	X	X	X	X	X	X	
Information on subsequent RA treatment										X

CRP=c-reactive protein; EQ-5D=Euro Quality of Life – 5Dimensions; ESR= erythrocyte sedimentation rate; HAQ-DI; Health Assessment Questionnaire-Disability Index; RA=rheumatoid arthritis; SJC=swollen joint count; TCJ=tender joint count; V=Visit; VAS=Visual Analogue Scale

[a] Only if assessed as per current clinical practice. Since this is a noninterventional study, no additional diagnostic or monitoring procedure will be applied.

[b] Visits are recommended to be quarterly.

[c] Written data consent will be obtained before any data are collected on study-specific forms. Written data consent may be obtained after the start of CZP treatment if the patient met all inclusion and exclusion criteria at the start of CZP treatment. For these patients, written data consent must be obtained at the start of Visit 2 and prior to conducting any clinical assessment at this visit.

5.3 Rationale for study design and selection of dose

This is an observational, noninterventional, noncomparative, postauthorization study to determine the use of CZP in adult patients with RA who are eligible for treatment with CZP according to the SmPC. This study was designed to assess the efficacy and long-term safety of CZP after 2 years of therapy. The selection of the dose will be determined by the patient's prescribing physician and procedures will follow standard clinical practice as defined in the SmPC. Since the number of patients included in this noninterventional study will add significantly to the existing safety data for CZP, this study is a PASS.

This study was designed to assess the efficacy and long-term safety of CZP after 2 years of therapy in daily practice. The selection of the dose will be determined by the patient's prescribing physician.

Since study patients will receive CZP in accordance with the SmPC guidance, the risk for the patients is not considered to be increased by their participation in this noninterventional study.

6 SELECTION AND WITHDRAWAL OF PATIENTS

6.1 Inclusion criteria

Patients must fulfill the following inclusion/exclusion criteria at the start of CZP treatment:

1. Before any data are collected on study-specific forms for a patient in this noninterventional PASS, written data consent will be properly executed and documented. The patient is informed and given ample time and opportunity to think about his/her participation and has given his/her written consent on the use of data.
   Note: A patient may be enrolled into the study after the start of CZP treatment if he/she met all inclusion and exclusion criteria at the start of CZP treatment. Written data consent must be obtained no later than the start of Visit 2 and prior to conducting any clinical assessment at Visit 2. Following written data consent (ie, enrollment into the study), all relevant data from original records will be entered onto study-specific forms.
2. Patient is considered reliable and capable of adhering to the observational plan (eg, able to understand and complete questionnaires, visit schedule, or medication administration according to the judgment of the treating physician.
3. Patient is male or female ≥18 years of age diagnosed with moderate to severe, active RA and is eligible for treatment with CZP therapy.
   Note: Patients enrolled into the study after the start of CZP treatment must have had a DAS28 score at the start of CZP treatment that is documented in their original records and indicates moderate to severe RA.
4. The decision to prescribe CZP has been made by the treating physician independently of his/her decision to include the patient in the study.
5. The patient's treatment must be within the terms of the SmPC.

6.2 Exclusion criteria

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

1. Patient has previously (before Visit 1) been treated with CZP
2. Patient has known hypersensitivity to any components of CZP

6.3 Withdrawal criteria

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

If a patient discontinues for any reason, this reason must be recorded on the Study Completion Form. The physician will be encouraged to invite the patients who discontinue CZP therapy early to return to the clinic/practice for posttreatment. A Safety Follow-Up Visit will be performed 84 days after administration of the last dose of CZP.

In case a patient withdraws his/her data consent no further data should be collected or submitted on this patient or caregiver. If a patient is institutionalized, this should be recorded on the medical update form. Follow-up of hospitalized patients should continue during hospitalization. Hospitalization, by itself, does not necessarily constitute a reason for discontinuation.

The treating physician is free to add or withdraw any kind of medication, or to withdraw the patient from the study at his/her own discretion.

7 STUDY TREATMENTS

7.1 Description of medicinal products

Certolizumab pegol will be provided on prescription from the treating physician.

7.2 Treatments to be administered

Patients will self-administer or be administered commercially available CZP according to standard clinical practice for the prescribing physician and as defined by the SmPC.

7.3 Packaging

The commercially available drug of CZP will be used with the trademark Cimzia®.

7.4 Labeling

Certolizumab pegol will be supplied as a commercially available product and as such will be labeled according to local requirements.

7.5 Handling and storage requirements

Certolizumab pegol will be provided upon prescription of the treating physician.

Certolizumab pegol must be stored in a refrigerator (2°C – 8°C) and must not be frozen. The prefilled syringe must be kept in the outer carton in order to be protected from light.

The patient must be instructed to store CZP out of the reach and sight of children.

The physician (or designee) will instruct the patient to store the medication following the instructions on the label.

7.6 Procedures for monitoring patient compliance

In accordance with standard clinical practice the treating physician or designee will assess compliance of CZP or other RA treatments at each contact with the patient. The information will be recorded in the observational form.

7.7 Concomitant medication(s)/treatment(s)

7.7.1 Permitted concomitant treatments (medications and therapies)

The treating physician is free to add, withdraw, or alter doses of any kind of medication at his/her own discretion based on standard medical practice and according to the marketing authorization. Refer to the treatment label for adequate prescription.

All concomitant medication and treatment must be recorded in the appropriate study documents (ie, observational form and source data).

The patient should be asked at each visit on new vaccinations received.

8 RECOMMENDED STUDY PROCEDURES BY VISIT

The schedule and the procedures of the study visit are recommended in accordance with the current clinical practice in this patient population. Data should be collected from a visit at the time nearest to that described in the schedule below.

8.1 Visit 1 (Week 0) Screening and/or Baseline

Prior to any study-specific activities, patients will be asked to read, sign, and date a data consent form. Patients will be given adequate time to consider any information concerning the study, given to them by the treating physician or designee. Patients will be prescribed antirheumatoid arthritis medication at the discretion of the treating physician.

The following data should be collected (if part of physicians' routine clinical practice):

- Demographics/medical history (including prior medical procedures related to RA)
- Presence of anti-cyclic citrullinated peptide antibodies (ACPA) or relevant rheumatic auto-antibodies
- RA history
- Prior and concomitant medication (including prior vaccinations)
- Drug administration
- Joint scores (28 count TJC, SJC)
- CRP or ESR
- Morning stiffness
- Physician's global assessment of disease activity using a VAS

- Patient's assessments
  - Patient's global assessment of disease activity using a VAS
  - Arthritis pain VAS
  - Fatigue Assessment Scale
  - HAQ-DI
  - EQ-5D
- Collect information on sick leave
- Employment status and employability due to RA

8.2 Visit 2 to Visit 9 (Week 6 to Week 104)

A patient may be enrolled into the study after the start of CZP treatment if he/she met all inclusion and exclusion criteria at the start of CZP treatment. Written data consent must be obtained no later than the start of Visit 2 and prior to conducting any clinical assessment at Visit 2. Following written data consent (ie, enrollment into the study), all relevant data from original records will be entered onto study-specific forms.

The following data should be collected (if part of physicians` routine clinical practice):

- Concomitant medication (including vaccinations)
- Concomitant medical procedures
- Adverse events
- Drug administration
- Joint scores (28-count TJC, SJC)
- CRP or ESR
- Morning stiffness
- Physician's global assessment of disease activity using a VAS
- Patient's assessments
  - Patient's global assessment of disease activity using a VAS
  - Arthritis pain VAS
  - Fatigue Assessment Scale
  - HAQ-DI
  - EQ-5D
- Collect information on sick leave
- Employment status and employability due to RA

8.3 Safety Follow-Up Visit (Week 116)

At Week 116 (or 84 days after the last treatment in the case of withdrawal), the following data should be collected (if part of physicians` routine clinical practice):

- Concomitant medication
- Adverse events
- Current RA treatment

9 ASSESSMENT OF EFFICACY

9.1 Arthritis Assessment

The joint assessment will be carried out on 28 joints. The 28 joints are shoulders, elbows, wrists (includes radiocarpal, carpal, and carpometacarpal bones which are to be considered as a single unit), metacarpophalangeal joints (MCP I, II, III, IV and V), thumb interinterphalangeal (IP) joints, proximal interphalangeals (PIP II, III, IV, and V) joints, and the knees.

Artificial and ankylosed joints are excluded from both tenderness and swelling assessments.

The swelling and the tenderness of each joint are graded on a 2–point scale as set out below:

Present	Swelling Response (28)	Tenderness Response (28)
No	None	Not tender
Yes	Detectable synovial thickening with or without loss of bony contours, or bulging synovial proliferation with or without cystic characteristics	Positive response to questioning (tender) spontaneous response elicited (tender and winced) or withdrawal by subject on examination (tender, winced, and withdrew)

9.2 Arthritis Pain VAS

Patients will rate how much pain they are experiencing at the time of the visit caused by their arthritis (ie, my pain at this time is) (see Appendix 16.1).

9.3 Patient's Global Assessment of Disease Activity Using a VAS

Patients will score their global assessment of their arthritis, in response to the question 'Considering all the ways your arthritis affects you, how are you feeling today?', using a VAS' (see Appendix 16.2).

9.4 Physician's Global Assessment of Disease Activity Using a VAS

The treating physician will assess the overall status of the patient with respect to the RA signs and symptoms and the functional capacity of the patient using a VAS. This assessment

by the physician must be made blind to the Patient's Global Assessment of Disease Activity (see Appendix 16.3).

9.5 Fatigue assessment scale

Patients will be asked to rate their fatigue during the past week on a numeric scale (see Appendix 16.4).

9.6 CDAI

The CDAI will be calculated using the sum of the tender and swollen joint counts and the Physician's and Patient's Global Assessment of Disease Activity.

The CDAI will not be calculated by the prescribing physician during the course of the study, but will be computed in the database for analysis purposes.

9.7 HAQ-DI

The HAQ-DI patient questionnaire (Fries et al, 1980 and Lautenschläger et al, 1997), which assesses the degree of difficulty experienced by the patient in 8 categories of daily living activities using 20 questions, is completed by the patient and checked by the treating physician for completeness (see Appendix 16.5).

9.8 DAS28

The DAS28 will be calculated using the tender and swollen joint counts, CRP, or ESR, and the Patient's Global Health Scale. The joint assessment will be carried out on 28 joints. The DAS28 will not be calculated by the prescribing physician during the course of the study but will be computed in the database for analysis purpose.

9.9 ACR/EULAR remission definition

The ACR and the EULAR suggested a provisional suggestion (Felson et al, 2011) based on a Boolean criterion. At any time point, a patient must satisfy all of the following:

2011 ACR/EULAR remission criteria:

- TJC ≤1
- SJC ≤1
- CRP ≤1mg/dL
- Patient's Global Assessment of Disease Activity (PtGADA) ≤10mm (on a scale of 0 to 100mm)

9.10 EQ-5D

Patients are asked to complete the entire document (5 questions + VAS, see Appendix 16.6) but only the VAS will be used to assess the change in health status measured as EQ-5D.

9.11 C-Reactive Protein and Erythrocyte Sedimentation Rate

C–reactive protein levels or ESR rate will be analyzed by a local laboratory. The preferred assessment is CRP; alternatively ESR can also be obtained, as long as the assessment is consistent throughout the course of the study.

9.12 Collection of Information on Sick Leave

Should the patient need to stay away from work at any time during the course of the study an accurate record must be kept in the patient's medical chart and the observational form. This record should include the duration of any sick leave and should also include the reason for the sick leave.

9.13 Employment status and employability due to RA

The patient should be asked at each visit on the current employment situation and employability due to RA. This record should include the type of employment or the reason for unemployment. Responses to each question must be reported in the patient's medical file.

9.14 Assessment of Morning Stiffness

The patient will be asked the duration of morning stiffness by the physician at each visit. Morning stiffness is the time elapsed between the time of usual awakening (even if not in the morning) and the time the patient is as limber as he/she will be during a day involving typical activities.

9.15 Presence of Rheumatoid Factor or Anti-cyclic Citrullinated Peptide Antibodies

The results of any previously recorded rheumatoid factors (RF) or anti-cyclic citrullinated peptide (aCCP) antibodies values are to be collected.

9.16 Drug Administration

The person administrating the drug (ie, self-administration vs. administration by others) and patient compliance (ie, number of missed doses) are to be recorded.

10 ASSESSMENT OF SAFETY

10.1 Adverse events

10.1.1 Definition of adverse event

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.

Patients will be assessed at all study visits including the Withdrawal Visit (if applicable) and at the Safety Follow-Up Visit 84 days after last dose of study medication. This includes all AEs not present prior to the initial visit and all AEs which recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the investigational product 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 treating physician from the patient's history or the Baseline Period.

Changes in scales and questionnaires will not be assessed as AEs.

Medical procedures will not be assessed as AEs; however, the reason for the procedure may be assessed as an AE.

10.1.1.1 Treatment emergent adverse events

The definition of a treatment emergent AE (TEAE) is an AE occurring within 5 half-lives of the last dose, or within 70 days.

10.1.1.2 Injection reactions

Injection reactions will also be recorded in the Noninterventional Observational Form. Injection reactions are classified as injection site reactions and systemic injection reactions.

An injection site reaction is any untoward medical event occurring at the injection site during or after study drug administration that can be at least possibly attributed to the study drug (ie, the relationship cannot be ruled out).
Examples: injection site pain, injection site burning, injection site erythema, injection site itching, injection site swelling.

A systemic injection reaction is any untoward medical hypersensitivity-like event other than injection site reaction, occurring during or after study drug administration that can be at least possibly attributed to the study drug. Systemic injection reactions are being further classified as acute and delayed based on timing and presentation of symptoms typical for hypersensitivity reactions.
Acute and delayed reactions to CZP should be reported according to the judgment of the Investigator, based on typical features, which include (but are not limited to) the following:

1. Acute injection reactions are usually defined as at least 1 of the following signs or symptoms occurring during or within 2 hours of the CZP infusion:

- Hypotension
- Urticaria
- Flushing
- Facial or hand edema
- Throat tightness, oral cavity or lip edema
- Headache
- Shortness of breath

2. Delayed injection reactions are usually defined as at least 2 of the following 4 signs or symptoms occurring within 1 to 14 days following the infusion:

- Rash
- Fever (more than 100°F [38°C])
- Polyarthralgias
- Myalgias

10.1.2 Procedures for reporting and recording adverse events

The patient 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 treating physician should review any self-assessment procedures (eg, questionnaires) that are employed in the study.

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact details for SAE reporting). The treating physician must forward to UCB (or its representative) a duly completed Adverse Event 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.

If clarifications on the AE are necessary, UCB 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 when applicable.

The Adverse Event Report form must be provided in English, all other requested information can be provided in German.

Additional information (eg, autopsy or laboratory reports) received by the treating physician 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 Adverse Event Report form. Translations into English will be done by the local Drug Safety department of UCB.

UCB has to perform an assessment of all AEs regarding seriousness and company causality. In case UCB upgrades a case to serious (death, life threatening, medically important event, hospitalization, significant/persistent disability, congenital anomaly), the physician will be informed. UCB also assesses a company causal relationship to CZP, independent of the physician's causal relationship.

The treating physician is specifically requested to collect and report to UCB (or its representative) any AEs, and to also inform participating patients of the need to inform the treating physician of any AE during the study.

10.1.3 Description of adverse events

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

10.1.4 Follow up on adverse events

An AE 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 (ie, cannot be contacted).

If an AE is still ongoing at the end of the study for a patient, follow up might be requested by the Drug Safety department of the Sponsor, depending on the nature of the AE. It 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 (ie, cannot be contacted).

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

Should a patient become pregnant after the administration of CZP during the course of the study, UCB’s local Drug Safety department should be informed immediately. The treating physician must inform the patient about the potential risk of malformations and about available alternatives, eg, voluntary termination with medical indication.

The pregnancy and the outcome (birth, miscarriage, 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 of the child. The health of the child and the mother must be followed for 30 days after birth for any significant medical issues.

Based on the child’s condition UCB may request that follow up be continued for a longer period even after end of the study.

In cases where the partner of a male patient enrolled in a noninterventional study 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.

10.1.7 Overdose of Cimzia

Excessive dosing (beyond that allowed according to marketing authorization) should be reported on the Adverse Event Report form. Any AE associated with excessive dosing must be followed as any other AE. These events may be symptomatic, in that the excessive dosing results in clinical signs and symptoms, or the excessive intake may itself be a symptom.

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 Cimzia so that investigators, 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 GCSP representative.

As appropriate for the stage of development and accumulated experience with Cimzia, medically qualified personnel at UCB may identify additional safety measures based on the safety review.

10.2 Serious adverse events

10.2.1 Definition of serious adverse event

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

- Results in death
- Is life-threatening
- Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.
- Results in significant or persistent disability/incapacity
- Is a congenital anomaly/birth defect (including that occurring in a fetus)
- Is an important medical event that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious
- Requires Initial inpatient hospitalization or prolongation of hospitalization
- A patient admitted to a hospital, even if 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 one 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 patient 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 criterion. 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.

- Important medical event

  An important medical event is defined as an AE that may not result in a serious outcome (ie, results in death, is life-threatening, requires hospitalization, results in a significant or persistent disability/incapacity, or results in a congenital anomaly/birth defect), but may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient or subject or may require medical or surgical intervention to prevent 1 of the serious outcomes listed above.
  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.

10.2.2 Procedures for reporting serious adverse events

If an SAE is reported, UCB Pharma must be informed within 24 hours of receipt of this information by the site (see contact numbers for SAE reporting listed in the Study Contact Information section). The physician must forward to UCB Pharma (or its representative) a duly completed physician SAE report form provided by UCB Pharma, 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 SAE report form will be provided to the physician. The physician SAE report form must be completed in German and will be translated in English by the Monitoring contract research organization (CRO).

The physician is specifically requested to collect and report to UCB Pharma (or its representative) any SAEs (even if the physician is certain that they are in no way associated with the investigational product), up to 84 days from the end of the study for each patient, and to also inform participating patients of the need to inform the physician of any AE within this period. Adverse events that the physician thinks may be associated with the investigational product must be reported to UCB Pharma regardless of the time between the event and the end of the study.

The reference document for the assessment of the expectedness of the AEs is the SmPC.

10.2.3 Follow up of serious adverse events

UCB Pharma (or its representative) may contact the physician to receive follow-up information on reported SAEs.

10.3 Adverse events of interest

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

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

10.4 Immediate reporting of AEs

The following AEs must be reported immediately, within 24 hours:

- SAE: AEs that the physician classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of interest, in case defined

10.5 Documentation of batch number

Based on current legislation from the German Regulatory Authority, the batch number should be documented for a biologic in the case of an AE or an SAE.

The batch number status ("batch number" or "batch number: unknown") should be documented on the AE page beside the handwritten notice.

The documentation of the batch number status ("batch number" or "batch number: unknown") should be in the appropriate field on the SAE page for SAEs.

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 Monitoring

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

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

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

11.1.1 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 (eg, 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 observational forms are not considered to be acceptable source documents.

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

11.1.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, patient files, laboratory notes). All data reported on the observational forms should be supported by source documents, unless otherwise specified.

11.2 Data handling

11.2.1 Observational form completion

The physician is responsible for the prompt reporting of accurate, complete, and legible data in the observational forms and in all required reports.

Any change or correction to the observational forms should be dated, initialed, and explained (if necessary) and should not obscure the original entry. Use of correction fluid is not permitted.

Corrections made after the physician’s review and signature of the completed observational forms will be resigned and dated by the physician.

The physician should maintain a list of personnel who are authorized to enter data into the observational forms.

Detailed instructions will be provided in the observational forms completion guidelines.

11.2.2 Database entry and reconciliation

Observational form/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 in order to check for discrepancies and to ensure consistency of the data.

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 Termination of the study

UCB Pharma 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.

If the study is prematurely terminated or suspended, UCB Pharma (or its representative) will inform the physicians/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 IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the physicians/institution, as specified by the applicable regulatory requirement(s).

11.4 Archiving and record keeping

The physician will maintain adequate records for the study including observational forms, medical records, laboratory results, if applicable, data consent documents, information regarding participants who discontinued, and other pertinent data.

UCB Pharma requires the documents to be retained at least for 10 years after completion of the study. The documents should be retained for a longer period if required by the applicable regulatory authorities. UCB Pharma will inform the physician/ institution when records no longer need to be retained. The physician will contact UCB Pharma for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The physician will also notify UCB Pharma should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's study master file.

11.5 Audit and inspection

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

The main purposes of an audit or inspection are to confirm that the rights and well-being of the patients enrolled have been protected, that enrolled patients (ie, those signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of CZP have been processed and reported in compliance with the planned arrangements, the observational plan, physician's site, and IEC SOPs, and applicable regulatory requirements.

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

12 STATISTICS

A description of statistical methods is presented below and will be described in more detail in the Statistical Analysis Plan.

12.1 Definition of analysis sets

The analysis set for the efficacy variables will be the Full Analysis Set. The Full Analysis Set is defined as all patients with a DAS28 ≥2.6 who took at least one dose of CZP and had at least one valid post-Baseline DAS28 value.

Note: the Full Analysis Set is defined in this way because patients who had a Baseline DAS28 value <2.6 would already be in remission. Therefore, the primary efficacy variable to reach clinical remission would not be defined.

The analysis set for the safety variables will be the Safety Set (SS), which is defined as all patients who took at least one dose of CZP.

12.2 General statistical considerations

Statistical analysis and generation of tables, figures, and subject data listings will be performed using SAS® Version 9.1.3 or higher. All statistical tables and listings will use Courier New, font size 9.

All variables will be analyzed in an explorative manner using descriptive statistics only. Summary statistics will consist of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, and median, standard deviation, minimum and maximum) will be tabulated.

For analyses by visit, visit will be used as documented.

The Baseline value for all analyzed variables is the measured value at Visit 1 (V1) in Week 0.

12.3 Planned efficacy analyses

12.3.1 Analysis of the primary efficacy variable

A patient is defined to have reached clinical remission if they show a DAS28 of <2.6. The absolute and relative number of patients in remission will be presented. Additionally, the respective 95% confidence interval (CI), constructed from an approximation to the Normal distribution, will be determined for the remission rate.

Evaluation will be done for subgroups defined by the following variables:

- Response at Visit 2 or Visit 3 (after approximately 6 and/or 12 weeks) defined by reduction in DAS28 by ≥1.2

- Presence of relevant auto-antibodies at Baseline (cut-off depends on test used, eg, immunoglobulin M-RF enzyme-linked immunosorbent assay: ≥0.110 optimetric density; Latextest: ≥20IU)
- Presence of anticytoplasmatic antibodies (aCCP antibodies or anti-mutated citrullinated vimentin [MCV]); threshold for aCCP positive patient at Baseline >50Units; threshold for anti-MCV positive patient at Baseline >50Units/mL
- Pretreatments with other anti-TNF agents
- Pretreatments with other biologics
- Duration of RA disease (<2 years vs. ≥2 years)

The remission rates between subgroups and their associated 95% CIs will be compared numerically only.

12.3.2 Analyses of secondary and other efficacy analyses

All variables will be analyzed using descriptive statistics as described above.

12.4 Planned safety and other analyses

12.4.1 Safety analyses

Safety will be assessed following company and local regulations on an observational basis. Safety variables will be listed individually for detailed clinical review, when needed. Safety analyses will be performed on the SS. Adverse events will be summarized descriptively by system organ class (SOC) and preferred term (PT). The most recent version of the Medical Dictionary for Regulatory Activities dictionary will be used. Additional tables will summarize AEs by seriousness and relationship to study drug as well as separate tables for AEs leading to withdrawal from the study or SAEs. The specific set of AEs reported as injection reactions will also be summarized descriptively by SOC and PT along with their classification between injection site reactions and systemic reactions (then later being further classified as acute or delayed). Abnormal laboratory values, as well as lack of efficacy, are not considered to be an AE unless the physician assesses it as such. Complications that are not considered as worsening of the underlying disease but as an AE need to be reported on the intended worksheet. The information collected from the patient reported outcomes (eg, EQ-5D, HAQ-DI, Fatigue Assessment Scale, and arthritis pain VAS) are only considered to be an AE if the physician classifies it as such.

12.4.2 Other analyses

None.

12.5 Handling of dropouts or missing data

Handling of dropouts or missing data will be described in detail in the Statistical Analysis Plan.

12.6 Planned interim analysis and data monitoring

The statistical analysis will proceed in several steps, based on interim analyses and a final analysis: interim analyses are planned to occur annually followed by a final analysis after

completion of the study. The SAS® databases created for the interim analyses will contain all available data collected by visit up to and including around Visit 3 (from first interim analysis on), and Visit 6 (from second analysis on and applicable for any further analyses). The final database will be locked after the last patient last visit and will contain all study data.

12.7 Determination of sample size

As no information on the expected remission rate for a 2-year study under real life conditions are available, an overall remission rate of 50%, which is the worst case for sample size calculation, was used for determination of sample size. Assuming this remission rate, a total of 1068 patients is sufficient to estimate with 95% confidence the overall remission rate with a precision of ±3.0%. Furthermore, subgroups of about 500 patients are sufficient to estimate the remission rate for each subgroup (as defined in Section 12.3.1) separately with an adequate precision (±4.5%).

In case the overall remission rate is much lower or higher (15% / 85%) a total of 1068 patients is sufficient to estimate with 95% confidence the overall remission rate with a precision of ±2.1%.

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 Data consent

Patient's data consent must be obtained and documented in accordance with local regulations, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

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

Prior to participation in the study, the written data consent form should be signed and personally dated by the patient and by the person who conducted the data consent discussion (physician [or designee]). The patient must receive a copy of the signed and dated data consent form.

A patient may be enrolled into the study after the start of CZP treatment if he/she met all inclusion and exclusion criteria at the start of CZP treatment. Written data consent must be obtained no later than the start of Visit 2 and prior to conducting any clinical assessment at Visit 2. Following written data consent (ie, enrollment into the study), all relevant data from original records will be entered onto study-specific forms.

As part of the consent process, each patient must consent to direct access to his/ her medical records for study-related monitoring, auditing, IEC review and inspections.

13.2 Patient Card

Patient card from the Doctor's Information Package should be handed out to each patient as instructed in the SmPC.

13.3 Independent ethics committees

The study will be conducted under the auspices of the ethics committee (EC) of Charité Berlin, as defined in local regulations, and in accordance to the local national laws and regulations applicable to noninterventional studies and with the ethical principles that have their origin in the Declaration of Helsinki.

Before initiating a study, the physician will have written and dated full approval from the EC of Charité Berlin. Since physicians in Germany are obliged to ask their appropriate "Ärztekammer" for advice in terms of vocational law (Berufsordnung für Ärzte), it is highly recommended to obtain written agreement from them.

The German health Authority (Paul Ehrlich Institut), the head organization of the compulsory health insurances (GKV Spitzenverband), the association of the Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung), and the European Medicine Agency and (Co-) Rapporteur for centrally authorized products will be notified of this study.

13.4 Patient privacy

UCB Pharma staff (or designee) will affirm and uphold the patient's confidentiality. Throughout this study, all data forwarded to UCB Pharma (or designee) will be identified only by an identification number.

The physician agrees that representatives of UCB Pharma, its designee, representatives of the relevant EC, or representatives of regulatory authorities will be allowed to review that portion of the patient's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, admission/discharge summaries for hospital admissions occurring during a patient'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.

Other than in emergency, all items in the protocol and amendment(s) are to be followed exactly. If an amendment is required, this must be made in written form and receive approval within UCB Pharma. Protocol amendment(s) will be distributed to physician(s) with instructions.

14 FINANCE, INSURANCE, AND PUBLICATION

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

15 REFERENCES

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German Medicines Act 14th and 15th Amendments Novelle des deutschen Arzneimittelgesetzes (AMG).

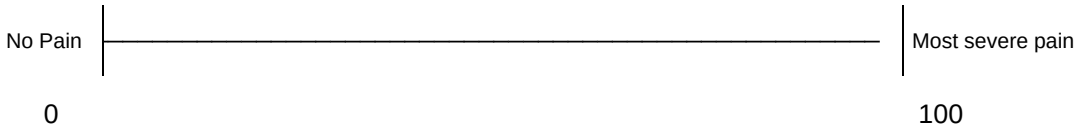
Lautenschläger J, Mau W, Kohlmann T, Raspe H, Struve F, Bruckle W, et al. Vergleichende Evaluation einer deutschen Version des Health Assessment Questionnaire (HAQ) und des Funktionsfragebogen Hannover (FFbH). Z Rheumatol. 1997 May-Jun;56(3):144-55.

16 APPENDICES

16.1 Patient's Assessment of Arthritis Pain

Patient's Assessment of Arthritis Pain

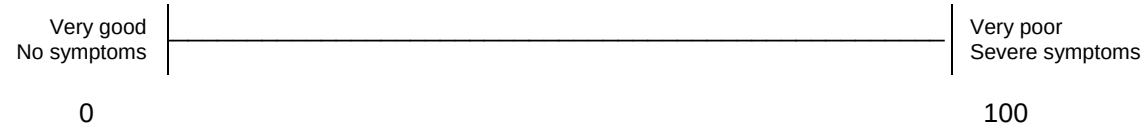
Please mark a vertical line on the scale below to show how much pain you are having from your arthritis today.



16.2 Patient's Global Assessment of Disease Activity

Patient's Global Assessment of Disease Activity

Considering all the ways your arthritis affects you, please mark a vertical line on the scale below to show how you are feeling today.



16.3 Physician's Global Assessment of Disease Activity

Physicians will be asked to assess the overall status of the subject's rheumatoid arthritis signs and symptoms and the functional capacity of the subject using a 100 mm Visual Analogue Scale (VAS) between 0 (Very Good) and 100 (Very Poor).

16.4 Fatigue Assessment Scale

Fatigue Assessment Scale

Please rate your fatigue (weariness, tiredness) **during the past 7 days**, on a scale of 0-10.

No Fatigue	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Fatigue as bad as you can imagine**

16.5 Health Assessment Questionnaire

HEALTH ASSESSMENT QUESTIONNAIRE

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
DRESSING & GROOMING Are you able to:				
- Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____
- Shampoo your hair?	_____	_____	_____	_____
ARISING Are you able to:				
- Stand up from a straight chair?	_____	_____	_____	_____
- Get in and out of bed?	_____	_____	_____	_____
EATING Are you able to:				
- Cut your meat?	_____	_____	_____	_____
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____
- Open a new milk carton?	_____	_____	_____	_____
WALKING Are you able to:				
- Walk outdoors on flat ground?	_____	_____	_____	_____
- Climb up five steps?	_____	_____	_____	_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Cane

_____ Walker

_____ Crutches

_____ Wheelchair

_____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)

_____ Built up or special utensils

_____ Special or built up chair

_____ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming

_____ Arising

_____ Eating

_____ Walking

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
HYGIENE Are you able to:				
- Wash and dry your body?	_____	_____	_____	_____
- Take a tub bath?	_____	_____	_____	_____
- Get on and off the toilet?	_____	_____	_____	_____
REACH Are you able to:				
- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	_____	_____	_____	_____
- Bend down to pick up clothing from the floor?	_____	_____	_____	_____

GRIP

Are you able to:

- Open car doors?	_____	_____	_____	_____
- Open jars which have been previously opened?	_____	_____	_____	_____
- Turn faucets on and off?	_____	_____	_____	_____

ACTIVITIES

Are you able to:

- Run errands and shop?	_____	_____	_____	_____
- Get in and out of a car?	_____	_____	_____	_____
- Do chores such as vacuuming or yardwork?	_____	_____	_____	_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

____ Raised toilet seat	____ Bathtub bar
____ Bathtub seat	____ Long-handled appliances for reach
____ Jar opener (for jars	____ Long-handled appliances in bathroom
previously opened)	____ Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

____ Hygiene	____ Gripping and opening things
____ Reach	____ Errands and chores

16.6 EQ-5D

Health Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

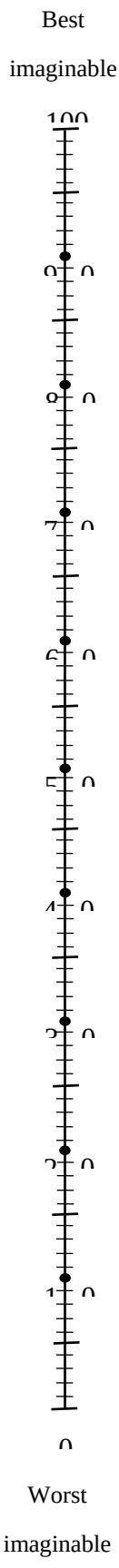
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



16.7 Protocol Amendment 1

Rationale for the amendment

In consideration of the instances that data consent cannot be obtained directly at Visit 1, patients will be allowed to enroll in this study after the start of CZP treatment. As a result, appropriate guidance was added throughout the protocol regarding the collection of written data consent, and the respective inclusion and exclusion criteria were updated.

Study contact information was updated to reflect a change in the Sponsor Study Physician and the addition of a CRO. The SAE reporting telephone and fax numbers were updated and an email address provided to reflect the addition of the CRO.

Vaccination status was removed as a study objective, other efficacy variable, and assessment of efficacy. Instead, information on prior and concomitant vaccinations will be collected with prior and concomitant medications and therapies. The assessment of concomitant medication was also removed as an assessment of efficacy.

Collection of the incidence of AEs was added as a safety variable.

Information on prior and concomitant medical procedures will be collected at Visit 1 and subsequent visits, respectively.

The names of the Patient's and Physician's Global Assessment of Arthritis VAS were changed to the Global Assessment of Disease Activity using a VAS for internal consistency.

The remainder of the changes in this amendment was administrative and is described in detail below.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- A patient may be enrolled into the study after the start of CZP treatment.
- Study contact information was updated to reflect a change in the Sponsor Study Physician and the addition of a CRO. The SAE reporting telephone and fax numbers were updated and an email address provided to reflect the addition of the CRO.
- The names of the Patient's and Physician's Global Assessment of Arthritis VAS were changed to the Global Assessment of Disease Activity using a VAS for internal consistency.
- Vaccination status was removed as a study objective, other efficacy variable, and assessment of efficacy. Instead, information on prior and concomitant vaccinations will be collected with prior and concomitant medications and therapies.
- The assessment of concomitant medication was removed as an assessment of efficacy.
- Collection of the incidence of AEs was added as a safety variable.

- Information on prior and concomitant medical procedures will be collected at Visit 1 and subsequent visits, respectively.

Specific changes

Change #1

Clinical Trial Protocol, page 4.

Sponsor Study Physician

Name:	[redacted]
Address:	Schwarz Biosciences GmbH Alfred-Nobel-Str. 10 40789 Monheim
Phone:	[redacted]
Fax:	[redacted]

Clinical Monitoring Contract Research Organization

Name:	
Address:	
Phone:	
Fax:	

Has been changed to:

Sponsor Study Physician

Name:	[redacted]
Address:	UCB GmbH Alfred-Nobel-Str. 10 40789 Monheim
Phone:	[redacted]
Fax:	[redacted]

Clinical Monitoring Contract Research Organization

Name:	Winicker Norimed GmbH
Address:	Deutschherrnstraße 15 – 19 90429 Nürnberg
Phone:	[redacted]
Fax:	[redacted]

Change #2

Clinical Trial Protocol, page 5. Telephone and fax numbers for SAE reporting were revised.

Serious Adverse Event reporting (24h), safety related issues		
• **Fax**	**Europe:** +32 2 386 24 21	
• **Phone**	**During business hours:**	**Outside business hours:**
	Europe: +32 2 386 24 68	**Europe:** +32 2 386 24 68

Has been changed to:

Serious Adverse Event reporting (24h), safety related issues		
• **Fax**	**Europe:** +49 911 926 804444	
• **Phone**	**During business hours:**	**Outside business hours:**
	Europe: +49 911 926 808777	**Europe:** +49 2173 48 0
• **Email**	Fast-sae@winicker-norimed.com	

Change #3

3.3 Other objectives

The following objective was deleted:

- Gather information on vaccination (type, time point, etc.)

Change #4

4.1.3 Other efficacy variables

The following variable was deleted:

- Vaccination status

Change #5

The following new section was added:

4.2 Safety variable

- Incidence of AEs

Change #6

5.1.1 Study duration

- Baseline Visit at onset of therapy (after deciding to treat the patient with CZP)

Has been changed to:

- Baseline Visit at onset of therapy (after deciding to treat the patient with CZP).
  Note: A patient may be enrolled into the study after the start of CZP treatment if he/she met all inclusion and exclusion criteria at the start of CZP treatment. Written data consent must be obtained no later than the start of Visit 2 and prior to conducting any clinical assessment at Visit 2. Following written data consent (ie, enrollment into the study), all relevant data from original records will be entered onto study-specific forms.

Change #7

5.2 Schedule of study assessments

Assessments[a]	**Treatment period**[b]									**Safety Follow-Up**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Week	**0**	**6**	**12**	**24**	**36**	**52**	**64**	**76**	**104**	**116**
Written Data Consent[c]	X									
Demographics / Medical History	X									
Presence of Rheumatoid Factor	X									
Presence of anti-cyclic citrullinated peptide antibodies	X									
RA history	X									
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Drug administration	X	X	X	X	X	X	X	X	X	
Joint scores (TJC, SJC) (28 joint count)	X	X	X	X	X	X	X	X	X	
Acute phase reactant (CRP or ESR)	X	X	X	X	X	X	X	X	X	
Morning stiffness	X	X	X	X	X	X	X	X	X	
Patient’s Global Assessment of	X	X	X	X	X	X	X	X	X	

Assessments[a]	Treatment period[b]									Safety Follow-Up
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Week	**0**	**6**	**12**	**24**	**36**	**52**	**64**	**76**	**104**	**116**
Arthritis VAS										
Physician's Global Assessment of Arthritis VAS	X	X	X	X	X	X	X	X	X	
Arthritis pain VAS	X	X	X	X	X	X	X	X	X	
Fatigue Assessment Scale	X	X	X	X	X	X	X	X	X	
HAQ-DI	X	X	X	X	X	X	X	X	X	
EQ-5D	X	X	X	X	X	X	X	X	X	
Sick leave	X	X	X	X	X	X	X	X	X	
Hospitalizations during previous 12 month	X					X			X	
Employment status and employability due to RA	X	X	X	X	X	X	X	X	X	
Information on subsequent RA treatment										X

CRP=c-reactive protein; EQ-5D=Euro Quality of Life – 5Dimensions; ESR= erythrocyte sedimentation rate; HAQ-DI; Health Assessment Questionnaire-Disability Index; RA=rheumatoid arthritis; SJC=swollen joint count; TCJ=tender joint count; V=Visit; VAS=Visual Analogue Scale

[a] Only if assessed as per current clinical practice. Since this is a noninterventional study, no additional diagnostic or monitoring procedure will be applied.

Assessments[a]	Treatment period[b]									Safety Follow-Up
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Week	**0**	**6**	**12**	**24**	**36**	**52**	**64**	**76**	**104**	**116**

1. Visits are recommended to be quarterly
2. Prior to dosing and any study specific procedures

Has been changed to:

Assessments[a]	Treatment period[b]									Safety Follow-Up
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Week	**0**	**6**	**12**	**24**	**36**	**52**	**64**	**76**	**104**	**116**
Written Data Consent[c]	X	X								
Demographics / Medical History	X									
Presence of Rheumatoid Factor	X									
Presence of anti-cyclic citrullinated peptide antibodies	X									
RA history	X									
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Drug administration	X	X	X	X	X	X	X	X	X	
Joint scores (TJC, SJC) (28 joint count)	X	X	X	X	X	X	X	X	X	
Acute phase reactant (CRP or ESR)	X	X	X	X	X	X	X	X	X	
Morning stiffness	X	X	X	X	X	X	X	X	X	

Assessments[a]	Treatment period[b]									Safety Follow-Up
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Week	**0**	**6**	**12**	**24**	**36**	**52**	**64**	**76**	**104**	**116**
Patient's Global Assessment of Disease Activity (VAS)	X	X	X	X	X	X	X	X	X	
Physician's Global Assessment of Disease Activity (VAS)	X	X	X	X	X	X	X	X	X	
Arthritis pain VAS	X	X	X	X	X	X	X	X	X	
Fatigue Assessment Scale	X	X	X	X	X	X	X	X	X	
HAQ-DI	X	X	X	X	X	X	X	X	X	
EQ-5D	X	X	X	X	X	X	X	X	X	
Sick leave	X	X	X	X	X	X	X	X	X	
Hospitalizations during previous 12 month	X					X			X	
Employment status and employability due to RA	X	X	X	X	X	X	X	X	X	
Information on subsequent RA treatment										X

CRP=c-reactive protein; EQ-5D=Euro Quality of Life – 5Dimensions; ESR= erythrocyte sedimentation rate; HAQ-DI; Health Assessment Questionnaire-Disability Index; RA=rheumatoid arthritis; SJC=swollen joint count; TCJ=tender joint count; V=Visit; VAS=Visual Analogue Scale

[a] Only if assessed as per current clinical practice. Since this is a noninterventional study, no additional diagnostic or monitoring procedure will be

Assessments[a]	Treatment period[b]									Safety Follow-Up
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Week	**0**	**6**	**12**	**24**	**36**	**52**	**64**	**76**	**104**	**116**

applied.

[b] Visits are recommended to be quarterly.

[c] Written data consent will be obtained before any data are collected on study-specific forms. Written data consent may be obtained after the start of CZP treatment if the patient met all inclusion and exclusion criteria at the start of CZP treatment. For these patients, written data consent must be obtained at the start of Visit 2 and prior to conducting any clinical assessment at this visit.

Change #8

6.1 Inclusion criteria

Patients must fulfill the following inclusion/exclusion criteria:

1. Before any data are collected for a patient in this noninterventional PASS, a written data consent will be properly executed and documented. The patient is informed and given ample time and opportunity to think about his/her participation and has given his/her written consent on the use of data.

3. Patient is male or female ≥18 years of age with RA and is eligible for treatment with CZP therapy (DAS28 >3.2) as defined by the SmPC.

Has been changed to:

Patients must fulfill the following inclusion/exclusion criteria at the start of CZP treatment:

1. Before any data are collected on study-specific forms for a patient in this noninterventional PASS, written data consent will be properly executed and documented. The patient is informed and given ample time and opportunity to think about his/her participation and has given his/her written consent on the use of data.
   Note: A patient may be enrolled into the study after the start of CZP treatment if he/she met all inclusion and exclusion criteria at the start of CZP treatment. Written data consent must be obtained no later than the start of Visit 2 and prior to conducting any clinical assessment at Visit 2. Following written data consent (ie, enrollment into the study), all relevant data from original records will be entered onto study-specific forms.

3. Patient is male or female ≥18 years of age with RA and is eligible for treatment with CZP therapy (DAS28 >3.2) as defined by the SmPC.
   Note: Patients enrolled into the study after the start of CZP treatment must have had a DAS28 score that was >3.2 prior to the start of CZP treatment that is documented in their original records.

Change #9

6.2 Exclusion criteria

1. Patient has previously been treated with CZP

Has been changed to:

1. Patient has previously (before Visit 1) been treated with CZP

Change #10

7.7.1 Permitted concomitant treatments (medications and therapies)

The following text was added:

The patient should be asked at each visit on new vaccinations received.

Change #11

8.1 Visit 1 (Week 0) Screening and/or Baseline

- Demographics / medical history
- Assessment of concomitant medication
- Physician's global assessment of arthritis VAS
- Patient's assessments
  - Patient's global assessment of arthritis VAS

Has been changed to:

- Demographics / medical history (including prior medical procedures)
- Prior and concomitant medication (including prior vaccinations)
- Physician's global assessment of disease activity using a VAS
- Patient's assessments
  - Patient's global assessment of disease activity using a VAS

Change #12

8.2 Visit 2 to Visit 9 (Week 6 to Week 104)

The following text was added:

A patient may be enrolled into the study after the start of CZP treatment if he/she met all inclusion and exclusion criteria at the start of CZP treatment. Written data consent must be obtained no later than the start of Visit 2 and prior to conducting any clinical assessment at Visit 2. Following written data consent (ie, enrollment into the study), all relevant data from original records will be entered onto study-specific forms.

Change #13

8.2 Visit 2 to Visit 9 (Week 6 to Week 104)

- Assessment of concomitant medication
- Physician's global assessment of arthritis VAS
- Patient's assessments
  - Patient's global assessment of arthritis VAS

Has been changed to:

- Concomitant medication (including vaccinations)
- Physician's global assessment of disease activity using a VAS
- Patient's assessments
  - Patient's global assessment of disease activity using a VAS

And the following was added:

- Concomitant medical procedures

Change #14

8.3 Safety Follow-Up Visit (Week 116)

- Assessment of concomitant medication

Has been changed to:

- Concomitant medication

Change #15

9.3 Patient's Global Assessment of Disease Activity VAS

Has been changed to:

9.3 Patient's Global Assessment of Disease Activity Using a VAS

Change #16

9.4 Physician's Global Assessment of Disease Activity VAS

This assessment by the physician must be made blind to the Patient's Global Assessment of Arthritis (see Appendix 16.3).

Has been changed to:

9.4 Physician's Global Assessment of Disease Activity Using a VAS

This assessment by the physician must be made blind to the Patient's Global Assessment of Disease Activity (see Appendix 16.3).

Change #17

The following section was deleted:

9.11 Assessment of Concomitant Medication

Should any treatment other than CZP be taken by the patient during the course of the trial (including over-the-counter products and nutraceuticals) an accurate record must be kept in the patient's medical chart and the observational form.

Change #18

The following section was deleted:

9.15 Vaccination status

The patient should be asked at each visit on new vaccinations received. This record should include the type of vaccination and any associated AEs.

Change #19

10.1.1 Definition of adverse event

The following was added:

Medical procedures will not be assessed as AEs; however, the reason for the procedure may be assessed as an AE.

Change #20

10.2.3 Follow up of serious adverse events

UCB may contact the physician to receive follow-up information on reported SAEs.

Has been changed to:

UCB (or its representative) may contact the physician to receive follow-up information on reported SAEs.

Change #21

13.1 Data consent

The following text was added:

A patient may be enrolled into the study after the start of CZP treatment if he/she met all inclusion and exclusion criteria at the start of CZP treatment. Written data consent must be obtained no later than the start of Visit 2 and prior to conducting any clinical assessment at Visit 2. Following written data consent (ie, enrollment into the study), all relevant data from original records will be entered onto study-specific forms.

16.8 Protocol Amendment 2

Rationale for the amendment

The "other efficacy variable" of hospital stays was deleted from the protocol because these data will no longer be collected. It was determined by the Sponsor that there was an unreasonable balance between the value of the information and the effort to retrieve it.

The Cimzia SmPC does not include nor is it foreseen to include a specific DAS28 score to identify moderate to severe, active RA; therefore, the requirement for DAS28>3.2 was deleted from an inclusion criterion.

Per the request of the German Regulatory Authority, the batch number status must be documented on the AE and SAE pages. Therefore, this information was added to the protocol.

Patients who discontinue CZP due to remission will not be followed; therefore, this sentence was deleted.

The time for follow-up of an AE was changed from 21 days to 12 weeks after the patient takes the last dose of medication, as this is considered to be a more appropriate amount of time. Guidance on AEs of interest, overdose, and safety signal detection was also added.

Other changes were administrative in nature to update Sponsor information and for internal consistency.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- "UCB GmbH" was changed to "UCB Pharma GmbH" to reflect the name change for the UCB German affiliate.
- References to "24 months" were changed to "2 years" for internal consistency.
- The criterion for low disease activity was changed from DAS28<3.2 to DAS28≤3.2.
- References to "normal" clinical practice were changed to "standard" clinical practice.
- The "other efficacy variable" of hospital stays was deleted.
- The portion of the inclusion criterion that specified a requirement for DAS28>3.2 was deleted.
- The time for follow-up of an AE was changed from 21 days to 12 weeks after the patient takes the last dose of medication.
- Collection of AE data was added in regards to overdose and AEs of special interest.
- Selected data from this study will be reviewed periodically for safety signal detection.
- Batch number status must be documented on the AE and SAE pages.

Specific changes

Change #1

Throughout the protocol, “UCB GmbH” was changed to “UCB Pharma GmbH” to reflect the name change for the UCB German affiliate.

Change #2

Sponsor Authorization

The persons named to the following roles have been changed:

[redacted]

Change #3

Study Contact Information

Clinical Trial Biostatistician

Name:	[redacted]
Address:	Schwarz Biosciences GmbH Alfred-Nobel-Str. 10 40789 Monheim
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Name:	[redacted]
Address:	Schwarz Biosciences GmbH Alfred-Nobel-Str. 10 40789 Monheim
Phone:	[redacted]
Fax:	[redacted]

Change #4

1 Summary

This is an observational, noninterventional, noncomparative, postauthorization safety study designed to assess the safety and efficacy of certolizumab pegol (CZP) in long-term use (24 months) in normal daily clinical practice. The observational nature of the study leaves the therapeutic decision exclusively within the discretion of the physician. Procedures and assessments are not to go beyond what is normal in clinical practice.

The maximum duration of participation for individual patients will be up to 116 weeks.

Has been changed to:

This is an observational, noninterventional, noncomparative, postauthorization safety study designed to assess the safety and efficacy of certolizumab pegol (CZP) in long term use (2 years) in standard daily clinical practice. The observational nature of the study leaves the therapeutic decision exclusively within the discretion of the physician. Procedures and assessments are not to go beyond what is standard in clinical practice.

The maximum duration of participation for individual patients will be 116 weeks.

Change #5

2 Introduction

This noninterventional, postauthorization safety study is designed to assess the efficacy and safety of CZP in long term use (24 months) in normal clinical practice according to the instructions for the use in patients with RA as described in the SmPC.

Certolizumab pegol is a recombinant, humanized antibody Fab′-fragment that is manufactured in *Escherichia coli*.

Certolizumab pegol is approved by the Food and Drug Administration for the treatment of adults with moderately to severely active RA.

Has been changed to:

This noninterventional, postauthorization safety study is designed to assess the efficacy and safety of CZP in long term use (2 years) in standard clinical practice according to the instructions for the use in patients with RA as described in the SmPC.

Certolizumab pegol is a recombinant, humanized antibody Fab′ fragment that is produced in an *Escherichia coli* expression system.

Certolizumab pegol is approved in the European Union, Switzerland, the United States, and Canada for the treatment of adults with moderately to severely active RA.

Change #6

3.3 Other objectives

- To evaluate and assess the effect of treatment over time with CZP for the following:
  - Pharmacoeconomic data (hospital stays, missing days at work, and employment information)

Has been changed to:

- To evaluate and assess the effect of treatment over time with CZP for the following:
  - Pharmacoeconomic data (missing days at work and employment information)

Change #7

4.1.3 Other efficacy variables

- Low disease activity (DAS28 of <3.2) by visit

Has been changed to:

- Low disease activity (DAS28 of ≤3.2) by visit

The following variable has been deleted:

- Hospital stays

Change #8

5.1.1 Study duration

The following sentence was deleted:

Patients who discontinue CZP due to remission will continue to be observed and data will continue to be collected at the above specified time points until Week 116.

Change #9

5.2 Schedule of study assessments

The following row for the hospitalizations during the previous 12 month has been deleted from the schedule of study assessments:

Assessments[a]	Treatment period[b]									Safety Follow-Up
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Week	**0**	**6**	**12**	**24**	**36**	**52**	**64**	**76**	**104**	**116**
Hospitalizations during previous 12 month	X					X			X	

Change #10

5.3 Rationale for study design and selection of dose

This is an observational, noninterventional, noncomparative postmarketing study to determine the use of CZP in adult patients with RA who are eligible for treatment with CZP according to the SmPC. This study was designed to assess the efficacy and long-term safety of CZP (use over 24 months). The selection of the dose will be determined by the patient's prescribing physician and procedures will follow normal clinical practice as defined in the SmPC. Since the number of patients included in this noninterventional study will add significantly to the existing safety data for CZP, this study is a PASS.

This study was designed to assess the efficacy and long-term safety of CZP (use over 24 months) in daily practice. The selection of the dose will be determined by the patient's prescribing physician.

Has been changed to:

This is an observational, noninterventional, noncomparative, postauthorization study to determine the use of CZP in adult patients with RA who are eligible for treatment with CZP according to the SmPC. This study was designed to assess the efficacy and long term safety of CZP after 2 years of therapy. The selection of the dose will be determined by the patient's prescribing physician and procedures will follow standard clinical practice as defined in the SmPC. Since the number of patients included in this noninterventional study will add significantly to the existing safety data for CZP, this study is a PASS.

This study was designed to assess the efficacy and long term safety of CZP after 2 years of therapy in daily practice. The selection of the dose will be determined by the patient's prescribing physician.

Change #11

6.1 Inclusion criteria

3. Patient is male or female ≥18 years of age with RA and is eligible for treatment with CZP therapy (DAS28 >3.2) as defined by the SmPC. Note: Patients enrolled into the study after

the start of CZP treatment must have had a DAS28 score that was >3.2 prior to the start of CZP treatment that is documented in their original records.

Has been changed to:

3. Patient is male or female ≥18 years of age diagnosed with moderate to severe, active RA and is eligible for treatment with CZP therapy. Note: Patients enrolled into the study after the start of CZP treatment must have had a DAS28 score at the start of CZP treatment that is documented in their original records and indicates moderate to severe RA.

Change #12

7.2 Treatments to be administered

Patients will self-administer or be administered commercially available CZP according to normal clinical practice for the prescribing physician and as defined by the SmPC.

Has been changed to:

Patients will self-administer or be administered commercially available CZP according to standard clinical practice for the prescribing physician and as defined by the SmPC.

Change #13

8.1 Visit 1 (Week 0) Screening and/or Baseline

- Demographics/medical history (including prior medical procedures)

Has been changed to:

- Demographics/medical history (including prior medical procedures related to RA)

Change #14

The following bullet has been deleted from 2 sections:

8.1 Visit 1 (Week 0) Screening and/or Baseline

8.2 Visit 2 to Visit 9 (Week 6 to Week 104)

- Collect information on hospitalizations (during previous 12 months)

Change #15

9.6 CDAI

The CDAI will be calculated using the tender and swollen joint counts, the Physician's and Patient's Global Assessment of Disease Activity, according to the following formula:

Swollen Joint Count + Tender Joint Count + Patient's Global Assessment of Disease Activity + Investigator's Global Assessment of Disease Activity

The joint assessment will be carried out on 28 joints. The 28 joints are the shoulders, elbows, wrists, MCP joints, PIP joints, and the knees. If joints are missing or not assessable, the number of joints will be weighted by the actual number of assessable joints.

The CDAI will not be calculated by the prescribing physician during the course of the trial, but will be computed in the database for analysis purposes.

Has been changed to:

The CDAI will be calculated using the sum of the tender and swollen joint counts and the Physician's and Patient's Global Assessment of Disease Activity.

The CDAI will not be calculated by the prescribing physician during the course of the study, but will be computed in the database for analysis purposes.

Change #16

The following section (previously Section 9.12) was deleted:

9.12 Collection of Information on Hospitalization

The patient will be asked at Visit 1, Visit 6, and Visit 9 on hospitalizations during the previous 12 months. In case of an affirmative answer, the record should include the reason for the hospitalization as well as the length of the hospital stay.

Change #17

10.1.4 Follow up on adverse events

If no follow up is provided, the physician must provide a justification. The follow up will be usually continued for 21 days after the patient has taken the last dose of medication.

Has been changed to:

If no follow up is provided, the physician must provide a justification. The follow up will be usually continued for 12 weeks after the patient has taken the last dose of medication.

Change #18

10.1.6 Pregnancy

Should a patient become pregnant after the first intake of CZP, UCB Global Clinical and Safety Pharmacovigilance should be informed immediately. The patient should be withdrawn from the study as soon as pregnancy is known and the following should be completed…

Has been changed to:

Should a patient become pregnant after the first intake of CZP, UCB Pharma or its representative should be informed immediately.

The patient should be withdrawn from the study as soon as pregnancy is known and the following should be completed…

Change #19

The following sections were added to the protocol:

10.1.7 Overdose of Cimzia

Any SAE or nonserious AE associated with excessive dosing must be followed as any other serious or nonserious AE. These events may be symptomatic, in that the excessive dosing results in clinical signs and symptoms, or the excessive intake may itself be a symptom.

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 Cimzia so that investigators, 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 GCSP representative.

As appropriate for the stage of development and accumulated experience with Cimzia, medically qualified personnel at UCB may identify additional safety measures based on the safety review.

Change #20

The following section was added to the protocol:

10.3 Adverse events of special interest

An AE of special interest is any AE that meets a 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."

The following AE's of special interest have been identified for Cimzia:

- Malignancies
- Serious infections (including opportunistic infections and tuberculosis)
- Serious hemorrhage
- Serious skin reactions (eg, Stevens Johnson syndrome, toxic epidermal necrosis, erythema multiforme)

Change #21

The following section was added to the protocol:

10.5 Documentation of batch number

Based on current legislation from the German Regulatory Authority, the batch number should be documented for a biologic in the case of an AE or an SAE.

The batch number status ("batch number" or "batch number: unknown") should be documented on the AE page beside the handwritten notice.

The documentation of the batch number status ("batch number" or "batch number: unknown") should be in the appropriate field on the SAE page for SAEs.

Change #22

13.2 Patient Card

Patient card from the Doctor's Information Package is supposed to be handed out to each patient (see SmPC).

Has been changed to:

Patient card from the Doctor's Information Package should be handed out to each patient as instructed in the SmPC.

16.9 Protocol Amendment 3

Rationale for the amendment

First interim analyses for data collected in RA0027 have shown that the quality of some of the data does not allow for the analyses of some of the originally determined variables. Furthermore, recent scientific evidence (Felson et al, 2011) suggests adding a new criterion for the assessment of clinical remission of RA. In addition, the focus of future interim analyses for RA0027 shifted from Week 104 towards Weeks 12 and 52, due to increased interest of the scientific community in short-term and medium-term response data. The resulting changes in study variables and in the purpose of future interim analyses (as compared to the situation prior to study start) are reflected in this protocol amendment.

A definition of treatment emergent AEs was added to increase the information content of the study protocol. For consistency across the CZP program, injection reaction definitions were added. The AEs of interest (formerly AEs of special interest) section was updated to be consistent with current reporting requirements.

Several subsections describing the assessment of safety were updated to be consistent with the latest wording used in study protocols for noninterventional studies.

In addition, the anticipated date for Last Patient Last Visit was brought forward to account for the current, promising recruitment status.

Minor changes were made to make the document more consistent with both the current UCB Submissions Style Guide and the current protocol template for noninterventional studies.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Administrative changes/corrections.
- Sponsor authorization and study contact information: Clinical Project Manager updated; Global Medical Affairs Medical Director updated; Clinical Program Director updated; Drug Safety Manager updated; Sponsor Study Physician updated; credentials added (where applicable).
- Updated the list of abbreviations.
- Updated the anticipated date for Last Patient Last Visit and shortened the anticipated overall study duration accordingly.
- Updated other efficacy variables to assess changes from Baseline in the quantity (rather than changes in doses) of concomitantly taken medications to meet the fact that in this observational, noninterventional study, exact doses of medications taken by the patients cannot be assessed. Updated the summary section to reflect update of other efficacy variables.

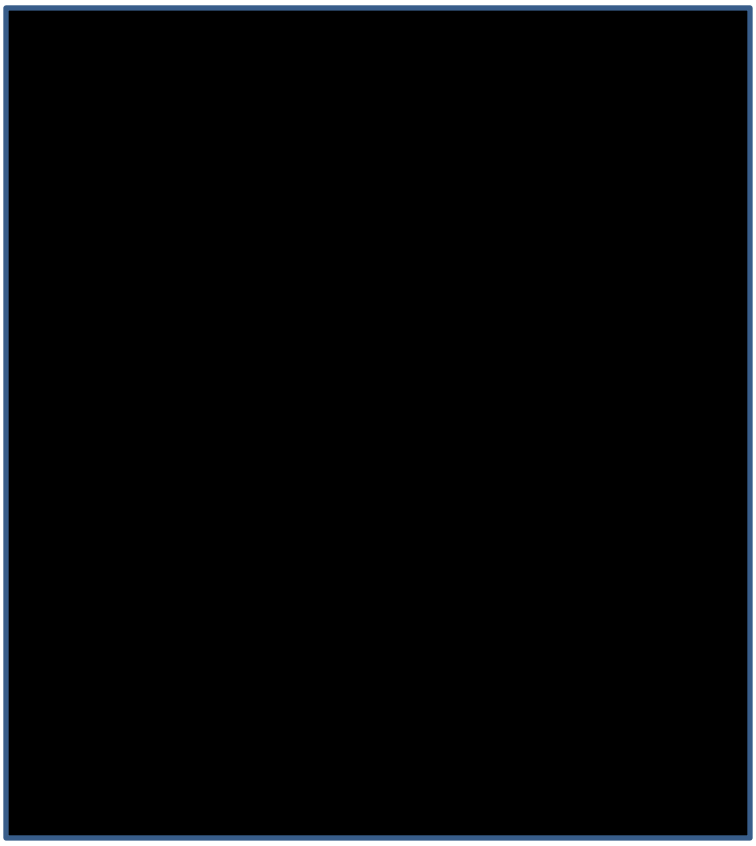
- Added the proportion of patients achieving clinical response and the assessment of clinical remission via ACR/EULAR criteria (ie, via the official, currently valid criteria to measure changes in RA symptoms) to other efficacy variables.
- Added definition of treatment emergent AEs and injection reactions to the AE section. Updated the duration of follow-up periods of 12 weeks to 84 days throughout the document to be consistent with the newly inserted Safety Follow-Up Period for AEs of 84 days.
- Updated the AE of interest (formerly AEs of special interest) section.
- Updated information on planned interim analyses.

Specific changes

Change #1

Sponsor authorization

Clinical Project Manager



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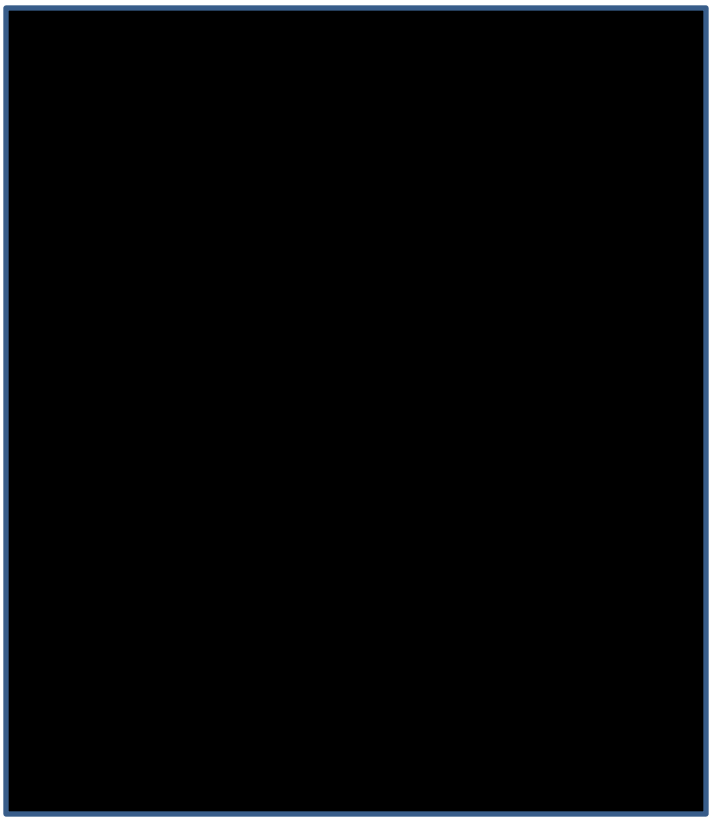
Date/Signature

Have been changed to:



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and

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Date/Signature

Have been deleted.

Change #2

Study contact information

Sponsor Study Physician

Name:	[redacted]
Address:	UCB Pharma GmbH Alfred-Nobel-Str. 10 40789 Monheim
Phone:	[redacted]
Fax:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	Schwarz Biosciences GmbH Alfred-Nobel-Str. 10 40789 Monheim
Phone:	[redacted]
Fax:	[redacted]

Have been changed to:

Sponsor Study Physician

Name:	[redacted]
Address:	UCB Pharma SA Allée de la Recherche 60 B-1070 Brussels BELGIUM
Phone:	[redacted]
Fax:	[redacted]

Clinical Project Manager

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

Change #3

List of abbreviations

The following abbreviations were added:

ACR	American College of Rheumatology
EULAR	European League Against Rheumatism
PtGADA	Patient's Global Assessment of Disease Activity
TEAE	treatment emergent adverse event

Change #4

1. Summary

The third paragraph:

The primary efficacy variable is clinical remission at Visit 9 (around Week 104) (defined as 28-joint count Disease Activity Score [DAS28 of <2.6]). Other efficacy variables include change from Baseline in patient's arthritis pain, levels of fatigue, health status, and physical functions assessed by the patient, clinical remission by visit, pharmacoeconomic information, and changes in the use of concomitant corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs).

Has been changed to:

The primary efficacy variable is clinical remission at Visit 9 (around Week 104) (defined as 28-joint count Disease Activity Score [DAS28 of <2.6]). Other efficacy variables include change from Baseline in patient's arthritis pain, levels of fatigue, health status, and physical functions assessed by the patient, clinical remission by visit, and pharmacoeconomic information.

And the second sentence in the last paragraph:

It is anticipated that the study will run from Q3 2009 (First Patient First Visit) to Q3 2015 (Last Patient Last Visit).

Has been changed to:

It is anticipated that the study will run from Q3 2009 (First Patient First Visit) to Q4 2014 (Last Patient Last Visit).

Change #5

3.3 Other objectives

The following objective:

- Assessment of clinical remission and low disease activity for all patients by visit and for different patient populations, based on DAS28

Has been changed to:

- Assessment of clinical remission and low disease activity for all patients by visit and for different patient populations, based on DAS28 and American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2011 remission criteria

Change #6

4.1.3 Other efficacy variables

The following variables:

- Change from Baseline in dose of concomitant DMARDs
- Change from Baseline in dose of concomitant corticosteroids

Have been changed to:

- Change from Baseline in quantity of concomitant DMARDs
- Change from Baseline in quantity of concomitant corticosteroids

In addition, the following variable:

- Change from Baseline in dose of NSAIDs

Has been deleted.

The following variables:

- Proportion of patients achieving clinical response to treatment based on DAS28 reduction of ≥1.2 by visit
- Proportion of patients in clinical remission as defined by the ACR/EULAR 2011 remission criteria

Have been added new.

Change #7

5.1.1 Study duration

The last sentence:

It is anticipated that study will be conducted from Q3 2009 to Q3 2015.

Has been changed to:

It is anticipated that this study will be conducted from Q3 2009 to Q4 2014.

Change #8

9.9 ACR/EULAR remission definition

The ACR and the EULAR suggested a provisional suggestion (Felson et al, 2011) based on a Boolean criterion. At any time point, a patient must satisfy all of the following:

2011 ACR/EULAR remission criteria:

- TJC ≤1
- SJC ≤1
- CRP ≤1mg/dL
- Patient's Global Assessment of Disease Activity (PtGADA) ≤10mm (on a scale of 0 to 100mm)

Have been added new.

Change #9

10.1.1 Definition of adverse event

The following subsections:

10.1.1.1 Treatment emergent adverse events

The definition of a treatment emergent AE (TEAE) is an AE occurring within 5 half-lives of the last dose, or within 70 days.

And

10.1.1.2 Injection reactions

Injection reactions will also be recorded in the Noninterventional Observational Form. Injection reactions are classified as injection site reactions and systemic injection reactions.

An injection site reaction is any untoward medical event occurring at the injection site during or after study drug administration that can be at least possibly attributed to the study drug (ie, the relationship cannot be ruled out).
Examples: injection site pain, injection site burning, injection site erythema, injection site itching, injection site swelling.

A systemic injection reaction is any untoward medical hypersensitivity-like event other than injection site reaction, occurring during or after study drug administration that can be at least possibly attributed to the study drug. Systemic injection reactions are being further classified as acute and delayed based on timing and presentation of symptoms typical for hypersensitivity reactions.
Acute and delayed reactions to CZP should be reported according to the judgment of the Investigator, based on typical features, which include (but are not limited to) the following:

1. Acute injection reactions are usually defined as at least 1 of the following signs or symptoms occurring during or within 2 hours of the CZP infusion:

- Hypotension
- Urticaria
- Flushing
- Facial or hand edema
- Throat tightness, oral cavity or lip edema
- Headache
- Shortness of breath

2. Delayed injection reactions are usually defined as at least 2 of the following 4 signs or symptoms occurring within 1 to 14 days following the infusion:

- Rash
- Fever (more than 100°F [38°C])
- Polyarthralgias
- Myalgias

Have been added new.

Change #10

10.1.2 Procedures for reporting and recording adverse events

To be consistent with the current template for noninterventional studies, the following text:

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact details for SAE reporting). The treating physician must forward to UCB (or its representative) a duly completed Adverse Event 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.

If clarifications on the AE are necessary, UCB 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 when applicable.

The Adverse Event Report form must be provided in English, all other requested information can be provided in German.

Additional information (eg, autopsy or laboratory reports) received by the treating physician 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 Adverse Event Report form. Translations into English will be done by the local Drug Safety department of UCB.

UCB has to perform an assessment of all AEs regarding seriousness and company causality. In case UCB upgrades a case to serious (death, life threatening, medically important event, hospitalization, significant/persistent disability, congenital anomaly), the physician will be informed. UCB also assesses a company causal relationship to CZP, independent of the physician's causal relationship.

The treating physician is specifically requested to collect and report to UCB (or its representative) any AEs, and to also inform participating patients of the need to inform the treating physician of any AE during the study.

Has been added new.

Change #11

10.1.4 Follow up on adverse events

To be consistent with the current template for noninterventional studies, the original text:

An AE 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 no follow-up is provided, the physician must provide a justification. The follow-up will be usually continued for 12 weeks after the patient has taken the last dose of medication.

Has been changed to:

An AE 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 (ie, cannot be contacted).

If an AE is still ongoing at the end of the study for a patient, follow up might be requested by the Drug Safety department of the Sponsor, depending on the nature of the AE. It 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 (ie, cannot be contacted).

Change #12

10.1.6 Pregnancy

To be consistent with the current template for noninterventional studies, the original text:

Should a patient become pregnant after the first intake of CZP, UCB Pharma or its representative should be informed immediately.

The patient should be withdrawn from the study as soon as pregnancy is known and the following should be completed:

- A Safety Follow-Up Visit should be scheduled 12 weeks after the patient has discontinued CZP.

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

In cases where the partner of a male patient enrolled in this observational study becomes pregnant, UCB Pharma will ask the physician or designee to contact the patient and his partner to request consent via the Partner Pregnancy Consent Form. If the partner agrees to provide additional information, the Pregnancy Report and Outcome Form will be forwarded to the patient's partner for completion.

The pregnancy will be documented on the Pregnancy Report and Outcome Form provided to the physician. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form upon which the physician has to report the health of the mother and of the child. The health of the child must be followed for 30 days after birth for any significant medical issues.

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

A pregnancy becomes a serious adverse event (SAE) in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child 'failure of a well followed contraception method'. Those SAEs must be additionally reported using the physician SAE Report form.

Has been changed to:

Should a patient become pregnant after the administration of CZP during the course of the study, UCB's local Drug Safety department should be informed immediately. The treating physician must inform the patient about the potential risk of malformations and about available alternatives, eg, voluntary termination with medical indication.

The pregnancy and the outcome (birth, miscarriage, 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 of the child. The health of the child and the mother must be followed for 30 days after birth for any significant medical issues.

Based on the child's condition UCB may request that follow up be continued for a longer period even after end of the study.

In cases where the partner of a male patient enrolled in a noninterventional study 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.

Change #13

10.1.7 Overdose of Cimzia

To be consistent with the current template for noninterventional studies, the original text:

Any SAE or nonserious AE associated with excessive dosing must be followed as any other serious or nonserious AE. These events may be symptomatic, in that the excessive dosing results in clinical signs and symptoms, or the excessive intake may itself be a symptom.

Has been changed to:

Excessive dosing (beyond that allowed according to marketing authorization) should be reported on the Adverse Event Report form. Any AE associated with excessive dosing must be followed as any other AE. These events may be symptomatic, in that the excessive dosing results in clinical signs and symptoms, or the excessive intake may itself be a symptom.

Change #14

10.2.1 Definition of serious adverse event

To be consistent with the current template for noninterventional studies, the following bullet point:

- Important medical event

  An important medical event is defined as an AE that may not result in a serious outcome (ie, results in death, is life-threatening, requires hospitalization, results in a significant or persistent disability/incapacity, or results in a congenital anomaly/birth defect), but may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient or subject or may require medical or surgical intervention to prevent 1 of the serious outcomes listed above.
  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.

Has been added new.

Change #15

10.3 Adverse events of special interest

Has been changed to:

10.3 Adverse events of interest

Furthermore, the original text:

An AE of special interest is any AE that meets a 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."

The following AE's of special interest have been identified for Cimzia:

- Malignancies
- Serious infections (including opportunistic infections and tuberculosis)
- Serious hemorrhage
- Serious skin reactions (eg, Stevens Johnson syndrome, toxic epidermal necrosis, erythema multiforme)

Has been changed to:

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," and "associated with the use of the drug." Adverse events of interest include:

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

Change #16

10.4 Immediate reporting of AEs

To be in line with the changes made in Section 10.3, the following bullet point:

- AE of special interest, in case defined

Has been changed to:

- AE of interest, in case defined

Change #17

12.6 Planned interim analysis and data monitoring

The next to last sentence:

The SAS® databases created for the interim analyses will contain all available data collected by visit up to and including around Visit 3 (from first interim analysis on), Visit 6 (from second interim analysis on), and Visit 9 (from third interim analysis on).

Has been changed to:

The SAS® databases created for the interim analyses will contain all available data collected by visit up to and including around Visit 3 (from first interim analysis on), and Visit 6 (from second analysis on and applicable for any further analyses).

Change #18

15 References

Felson DT, Smolen JS, Wells G, Zhang B, van Tujl LHD, Funovits J, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum. 2011;63:573-86.

Has been added new.

17 DECLARATION AND SIGNATURE OF PHYSICIAN

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 subphysicians 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.

Physician:

_____	_____
Printed Name	Date/Signature