PROTOCOL RA0043 AMENDMENT 9

A MULTICENTER, OPEN-LABEL STUDY TO ASSESS THE PHARMACOKINETICS, SAFETY, AND EFFICACY OF CERTOLIZUMAB PEGOL IN CHILDREN AND ADOLESCENTS WITH MODERATELY TO SEVERELY ACTIVE POLYARTICULAR-COURSE JUVENILE IDIOPATHIC ARTHRITIS

PASCAL (Pediatric Arthritis Study of CertolizumAb pegoL)

PHASE 3

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse events of special interest
ADCC	antibody-dependent cell-mediated cytotoxicity
ADA	adalimumab
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibodies
AST	aspartate aminotransferase
anti-dsDNA	anti-double-stranded deoxyribonucleic acid
BCG	Bacille Calmette-Guérin
CDMS	clinical data management system
CDC	Centers for Disease Control and Prevention
CDP870	certolizumab pegol
CHAQ	Childhood Health Assessment Questionnaire
CI	confidence interval
CID	Clinically Inactive Disease
COX-2	cyclooxygenase-2
CRF	case report form
CPM	Clinical Project Manager
CRM	clinical remission on medication
CRO	contract research organization
CRP	C-reactive protein
CTS	Clinical Trial Supplies
CZP	certolizumab pegol
DIP	distal interphalangeals
DMARD	disease-modifying antirheumatic drug
DMS	duration of morning stiffness
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
ECLIA	electrochemiluminescence immunoassay

ELISA	enzyme-linked immunosorbent assay
ERA	enthesitis-related arthritis
ES	Enrolled Set
ETN	etanercept
Fab′	fragment antigen binding
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPS-R	Faces Pain Scale-Revised
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ia	intra-articular
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation
IEC	independent ethics committee
IGRA	interferon-gamma release assay
im	intramuscular
IMP	investigational medicinal product
INH	isonicotinic acid hydrazide/isoniazid
IRB	institutional review board
iv	intravenous(ly)
IXRS	interactive voice/web response system
JADAS	Juvenile Arthritis Disease Activity Score
JIA	juvenile idiopathic arthritis
LOCF	last observation carried forward
LOM	limitation of motion
LTB	latent tuberculosis

LTBI	latent tuberculosis infection
MAR	missing at random
MCP	metacarpal
MedDRA®	Medical Dictionary of Regulatory Activities
MSD	Meso Scale Discovery
MTP	metatarsophalangeal
MTX	methotrexate
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
NTMB	nontuberculous mycobacteria
OC	observed case
PD	Pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PedACR30, 50, 70, 90	American College of Rheumatology Pediatric 30%, 50%, 70%, 90%
PEG	polyethylene glycol
PFS	prefilled syringe(s)
PIP	proximal interphalangeal
PK	pharmacokinetics
PK-PD	Pharmacokinetic-Pharmacodynamic
PK-PP	Pharmacokinetic Per-Protocol
POM	pain on motion
PopPK	population pharmacokinetic
PRN	as needed
PRINTO/PRCSG	Paediatric Rheumatology INternational Trials Organisation/ Pediatric Rheumatology Collaborative Study Group
Q2W, Q4W	every 2 weeks, every 4 weeks
RA	rheumatoid arthritis
RBC	red blood cell
RDC	remote data capture
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SDV	source data verification
SOP	standard operating procedures

SS	Safety Set
TB	tuberculosis
TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
USA	United States of America
VAS	visual analog scale
WBC	white blood cell

1 SUMMARY

This is a Phase 3, multicenter, open-label study to assess the pharmacokinetics (PK), safety, and efficacy of certolizumab pegol (CDP870, CZP, Cimzia®) in children and adolescents with moderately to severely active polyarticular-course juvenile idiopathic arthritis (JIA).

Certolizumab pegol, the investigational medicinal product (IMP), is a humanized antibody fragment antigen binding (Fab′), with specificity for human tumor necrosis factor alpha (TNFα), conjugated to polyethylene glycol (PEG). The drug intended for use in this study is the liquid formulation in a prefilled syringe (PFS).

The study population will consist of study participants 2 to 17 years of age upon enrollment with a minimum weight of 10kg (22lb). Study participants must have had onset of signs and symptoms consistent with polyarticular-course JIA and initiation of JIA treatment for at least 6 months prior to Baseline. Active polyarticular-course JIA disease is defined as ≥5 joints with active arthritis including: polyarthritis rheumatoid factor-positive, polyarthritis rheumatoid factor-negative, extended oligoarthritis, juvenile psoriatic arthritis, and enthesitis-related arthritis (ERA). Study participants cannot have had active uveitis within the last 6 months prior to Baseline. In addition, study participants must have had an inadequate response to, or intolerance to, at least 1 disease-modifying antirheumatic drug (DMARD).

The study consists of a Screening Period of up to 4 weeks; eligible study participants will then enter an open-label Treatment Period which will continue until the approval of the marketing application for the indication of polyarticular-course JIA in the study participant's country or region or until further notice from UCB. A Final Visit will be conducted 12 weeks after last dose of study medication.

Approximately 195 study participants are planned to be screened to enroll 156 study participants in this study, as follows:

- A minimum of 10 study participants will be enrolled on the reduced CZP dose regimen (Protocol Amendment 5) in each weight range of 10 to <20kg (22 to <44lb), 20 to <40kg (44 to <88lb), and ≥40kg (≥88lb).
- A minimum of 10 study participants will be enrolled in each age category of 2 to 5 years, 6 to 11 years, and 12 to 17 years, irrespective of the dose regimen.
- A minimum of 25 study participants will be enrolled who receive CZP as monotherapy (ie, study participants with established intolerability or inadequate response to MTX), irrespective of the dose regimen.
- A minimum of 10 study participants with ERA will be enrolled, irrespective of the dose regimen.

Each of these categories is assessed independently. In order to further support the safety assessment of the original CZP dose, as more of the safety data collected in the study to date has been on the reduced dose, an additional 30 study participants will be enrolled on the original dose regimen with the aim to enroll at least 5 study participants in each weight range of 10 to <20kg (22 to <44lb), 20 to <40kg (44 to <88lb), and ≥40kg (≥88lb) following Protocol Amendment 9.

A full interim analysis will be performed after all active study participants have completed the Week 24 (Visit 10) assessments.

Certolizumab pegol will be administered as a fixed dose based on weight throughout the study consisting of 3 loading doses at Weeks 0, 2, and 4, followed by maintenance doses Q2W. The original minimum and maximum loading doses in the study were CZP 100mg Q2W and CZP 400mg Q2W, respectively, and the original minimum and maximum maintenance doses were CZP 50mg Q2W and CZP 200mg Q2W, respectively. Based on an interim PopPK analysis of RA0043 data, the minimum and maximum loading doses in the study were adjusted to CZP 50mg Q2W and CZP 200mg Q2W, respectively, and the minimum and maximum maintenance doses were adjusted to CZP 50mg Q4W and CZP 100mg Q2W, respectively, following implementation of Protocol Amendments 4 and 5.

However, it was later determined that there were deficiencies detected with the use of the bioanalytical assay within RA0043, which rendered the PK data for the PopPK analysis and simulations that informed the dose reduction in Protocol Amendment 4 and 5 unusable from a regulatory standpoint. Accordingly, PK samples were no longer collected for study participants on the reduced CZP dose regimen following implementation of Protocol Amendment 8.

An electrochemiluminescence immunoassay (ECLIA) method, for which selectivity had previously been assessed in the RA matrix, has now been validated to meet the standards set in the regulatory guidance for analytical procedures and methods validations for drugs and biologics.

Based on 24-week interim results from the first 163 participants enrolled in RA0043, both the original and reduced dose regimens showed safety profiles similar to the approved CZP dose regimen in the adult RA population. The overall clinical response in this analysis (taking both dose regimens into account) was American College of Rheumatology Pediatric 30% (PedACR30) and PedACR50 responses of 77.3% and 67.5%, respectively at Week 12. The response from the original dose regimen was 75.6% for PedACR30 and 64.1% for PedACR50. PedACR50 response demonstrates a highly clinically relevant decrease in disease activity.

Therefore, in order to adequately assess the exposure levels and clinical experience of CZP in JIA at both the reduced and original CZP dose regimens and also adequately support the safety assessment of the original CZP dosing regimen, as more of the safety data collected in the study to date has been on the reduced dose, 30 additional study participants will be enrolled on the original CZP dose regimen following Protocol Amendment 9. All study participants enrolled following Protocol Amendment 9 will have plasma concentrations of CZP and anti-CZP antibodies analyzed using the ECLIA method. In addition, PK and ADA samples (for which sufficient volume is available) collected in this study prior to Protocol Amendment 9 will be analyzed with the ECLIA method. The collective ECLIA-based PK data for this study will form the basis of any future CZP modeling and simulation work.

The primary objectives of the study are to evaluate the PK and safety including the immunogenicity of CZP administered subcutaneously (sc) in children and adolescents with

moderate to severe polyarticular-course JIA. The primary PK and immunological variables are CZP plasma concentrations and anti-CZP antibody levels at Week 16 and Week 48.

The primary safety variables are the incidence of serious treatment-emergent adverse events (TEAEs) and TEAEs leading to permanent withdrawal of IMP. Other safety variables to be assessed are the incidence of TEAEs, vital signs and measurements of laboratory parameters including hematology, biochemistry, and urinalysis. Physical examination findings (except joint examination) are recorded in the case report form (CRF) only at Screening. Subsequent physical examinations are performed to assess clinically significant changes and thus, only abnormal findings are recorded in the CRF as AEs. Tanner stages (except growth) and growth (height, weight) over the course of the study will be assessed. Autoantibody (antinuclear antibodies [ANA] and anti-double-stranded deoxyribonucleic acid [anti-dsDNA] antibodies) concentrations will be evaluated. The secondary objective of the study is to assess the effectiveness of CZP on the clinical response in children and adolescents with moderate to severe polyarticular-course JIA.

The following efficacy variables are defined as secondary variables: PedACR30, PedACR50, PedACR70, and PedACR90 response rates at Week 16 (compared to Baseline). Other efficacy and health outcomes variables include: PedACR30, PedACR50, PedACR70, and PedACR90 response rates at other timepoints than Week 16 (compared to Baseline), change from Baseline in number of joints with active arthritis, change from Baseline in number of joints with limitation of range of motion, change from Baseline in Physician's Global Assessment of Disease Activity (visual analog scale [VAS]), change from Baseline in Childhood Health Assessment Questionnaire (CHAQ, parent/caregiver reported) total score, change from Baseline in Parent's Assessment of Arthritis Pain (VAS), change from Baseline in Parent's Global Assessment of Overall Well-Being (VAS), ratio to Baseline in C-reactive protein (CRP), change from Baseline in Juvenile Arthritis Disease Activity Score (JADAS), percentage of study participants meeting criteria of Clinically Inactive Disease (CID) and clinical remission on medication (CRM), time to CID, time to CRM, change from Baseline in duration of morning stiffness (DMS), change from Baseline in Faces Pain Scale-Revised (FPS-R, child reported, ages 5 to 11 years), change from Baseline in Patient's Assessment of Arthritis Pain (JIA Pain VAS, child reported, ages 12 to 17 years), change from Baseline in Fatigue Assessment Scale, and Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey (parent/caregiver reported).

2 INTRODUCTION

Certolizumab pegol (CDP870, CZP, Cimzia®) is approved in the United States of America (USA), the European Union, and a number of other countries worldwide for the treatment of moderately to severely active RA in adults.

Juvenile idiopathic arthritis is the clinical presentation of persistent arthritis (≥6 weeks in duration) of unknown etiology due to chronic inflammation of the synovium (Ravelli and Martini, 2007; Nigrovic and White, 2006). Juvenile idiopathic arthritis is the most commonly diagnosed rheumatic disease affecting children less than 16 years of age with a prevalence of approximately 100 in 100,000 children (Zitelli et al, 2012). Disease onset is typically by 5 years of age but rarely before 6 months, and females are affected approximately twice as frequently as males. Juvenile idiopathic arthritis leads to significant functional and emotional disability with 50% of affected children continuing to suffer from persistent inflammation and disability as adults.

The disease is characterized by B-cell, T-cell, and macrophage infiltration and expansion which leads to the release of proinflammatory cytokines and promotes synovial proliferation, resulting in thickened pannus and subsequently joint destruction. Patients with polyarticular-course JIA have ≥5 inflamed joints over the course of the disease. For the purpose of this study, polyarticular-course is defined as ≥5 joints at the time of enrollment. In addition to the articular manifestations, children with JIA commonly present with constitutional symptoms such as anorexia, weight loss, and growth failure.

The introduction of TNF-antagonists represented a major advance in the drug treatment of RA for adults and subsequently, JIA in children and adolescents. Two TNF-antagonists, etanercept (ETN) and adalimumab (ADA), are currently registered in both the USA and Europe for the treatment of JIA. The therapeutic response to these available TNF-antagonists is variable. This is also true for tolerability and is in keeping with the well known idiosyncratic response to traditional DMARDs. Therefore, a medical need remains for additional effective TNF-antagonists in the treatment of JIA.

TNFα blockers appear to be less effective in patients with systemic JIA compared to other JIA subtypes (Lovell et al, 2000). Recent evidence suggests that, unlike other JIA subtypes, abnormalities in the cytokines IL-1 and IL-6 play a major role in the pathogenesis of systemic JIA (Vastert et al, 2009). The IL-6 blocker tocilizumab is currently approved in the EU for systemic JIA (Tocilizumab [RoActemra®] Summary of Product Characteristics, 2010).

Certolizumab pegol is a humanized antibody antigen-binding fragment (Fab′), with specificity for human TNFα, which is conjugated to PEG. Certolizumab pegol has a high affinity for TNFα with a Kd of 0.9×10^{-10}M and has been shown to be an effective TNF-inhibitor, preventing the development of arthritis as assessed by both disease activity and joint histology in a transgenic mouse model of progressive arthritis. Certolizumab pegol does not neutralize TNF beta (lymphotoxin) and does not effect antibody-dependent cell-mediated cytotoxicity (ADCC) or activate complement-mediated lysis in vitro.

Single-dose and subchronic toxicity studies in animal models indicate that CZP was well tolerated and had no safety issues. Genotoxicity (in vitro and in vivo) and reproductive

toxicity (animal models) studies support the safety of the product, demonstrating no adverse effects from CZP.

Single intravenous (iv) and sc doses of CZP have been shown to have predictable dose-related exposure with an approximately linear relationship between the dose administered and both the maximum plasma concentration (C_{max}) and the area under the CZP plasma concentration versus time curve (AUC). The terminal elimination phase half-life is approximately 14 days. Certolizumab pegol has been demonstrated to have good bioavailability (~80%) when given sc.

No clinically meaningful drug-drug interactions between CZP and methotrexate (MTX) or its metabolite, 7-hydroxy MTX, have been detected. Population PK analyses have shown that concomitant administration of MTX (or other immunosuppressants), corticosteroids, aminosalicylic acid analogs, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or anti-infectives do not impact the PK of CZP. Age and gender had no effect on the PK of CZP in these studies. The influence of renal impairment was not studied as almost 80% of the study participants had a normal creatinine clearance and less than 2% of the study participants exhibited moderate to severe renal impairment.

The overall clinical efficacy of CZP studied both as monotherapy as well as concomitantly with MTX in MTX-inadequate responders, in the treatment of adult study participants with moderate to severe active RA, was demonstrated in four Phase 3 placebo-controlled RA studies. The dosing regimens tested included CZP 400mg sc at Weeks 0, 2, and 4 followed by CZP 200mg or CZP 400mg given Q2W with MTX and CZP 400mg every 4 weeks with and without MTX. Inhibition of the progression of structural damage was demonstrated in the two Phase 3 studies in which it was evaluated. Significant improvements in physical function, health-related quality of life (including pain and tiredness), and productivity within and outside the home were demonstrated with CZP compared with the control groups in all four Phase 3 studies.

Overall, the incidence and pattern of the treatment-emergent AEs observed in the Phase 3 studies of CZP in RA are consistent with those expected for RA patients on TNF-antagonist therapy and for this population as a whole and demonstrate that CZP has a favorable risk-to-benefit profile.

The risks of the present study are essentially those of experiencing an AE following administration of CZP and for progressive disability if the study participant does not respond to CZP. As a therapeutic class, currently available TNF-antagonists are known to be associated with serious infections, particularly reactivation of tuberculosis (TB) and opportunistic fungal infections. An association has also been reported with TNF-antagonist therapy and the development of lymphoma and leukemia especially in children and adolescents, although it is not clear whether there is a causal relationship as confounding factors exist (eg, the increased risk of lymphoma and leukemia associated with autoimmune diseases and immunosuppression) themselves. Other cancer types also have been reported in association with TNF-antagonist use, but the causal relationship for these is unclear as well. Other serious AEs that have been infrequently reported in patients treated with currently available TNF-antagonists including CZP include congestive heart failure, drug-induced lupus, demyelinating disorders, and pancytopenia.

In a placebo-controlled clinical study of study participants with RA, no meaningful difference was detected in antibody response to vaccine between CZP and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with CZP. Similar proportions of study participants developed protective levels of anti-vaccine antibodies between CZP and placebo treatment groups. Study participants receiving MTX had a lower humoral response compared with study participants not receiving MTX, with or without CZP. The clinical significance of this is unknown. Certolizumab pegol does not suppress the humoral immune response to the pneumococcal polysaccharide vaccine or influenza vaccine.

No data are available on the response to live vaccinations or the secondary transmission of infection by live vaccines in study participants receiving CZP. Live or live attenuated vaccines should not be administered concurrently with CZP.

Additional information on the nonclinical and clinical data for CZP in RA is available in the current version of the CZP Investigator's Brochure (IB).

Conducting placebo-controlled studies in pediatric populations requires special consideration. These include ethical concerns associated with denying active treatment to a population of patients that cannot make their own fully-informed choices about healthcare, the enrollment difficulties commonly encountered for placebo-controlled pediatric studies, and the limited size of the patient population from which to recruit. Studies in JIA are no exception for these considerations.

For the 2 TNF-antagonists (ETN and ADA) approved in the USA and Europe for the treatment of JIA, similarities between the adult RA and the JIA population were shown in the placebo-controlled clinical studies with respect to efficacy, safety, and dosing. In light of these results and the efficacy of CZP demonstrated in the 4 adequate and well-controlled studies in adult RA, it is appropriate to extrapolate these efficacy data to the intended JIA population if similar results are obtained for PK and safety in JIA as seen for adult RA. The opinion within the pediatric rheumatology community supports that extrapolation from open-label PK/safety data is acceptable for additional members of the class of TNF-antagonists.

3 STUDY OBJECTIVES

3.1 Primary study objectives

The primary objectives of the study are to evaluate the PK and safety including the immunogenicity of CZP administered sc in children and adolescents with moderate to severe polyarticular-course JIA.

3.2 Secondary study objective

The secondary objective of the study is to assess the effectiveness of CZP on the clinical response in children and adolescents with moderate to severe polyarticular-course JIA.

3.3 Other objectives

Other objectives of the study are to further assess safety as well as efficacy and health outcomes.

4 STUDY VARIABLES

See Section 13.1 for the definition of analysis sets.

4.1 Primary variables

4.1.1 Pharmacokinetic and immunological variables

Certolizumab pegol plasma concentrations and anti-CZP antibody levels at Week 16 and Week 48 will be assessed and data will be summarized.

4.1.2 Safety variables

The primary safety variables will be the incidence of serious TEAEs and TEAEs leading to permanent withdrawal of IMP.

Adverse events will be solicited at every visit, recorded and coded according to Medical Dictionary for Regulatory Activities (MedDRA®) criteria.

4.2 Secondary variables

Efficacy will be assessed by the PedACR30, PedACR50, PedACR70, and PedACR90 response rates at Week 16 as compared to Baseline (see Section 11.1 for definition).

4.3 Other variables

Other PK and immunological variables are:

- Certolizumab pegol plasma concentrations and anti-CZP antibody levels at other study timepoints

Other safety variables are:

- Incidence of TEAEs, TEAEs of interest, TEAEs by relatedness, TEAEs by severity, and TEAEs by duration of exposure
- Clinical laboratory values (hematology, biochemistry, and urinalysis) will be collected and assessed at every visit except Visits 3 and 4 and Unscheduled Visits.
- Vital sign abnormalities will be evaluated at every visit.
- Assessments of study participant's developmental stages and growth (height, weight) will be performed to determine Tanner stages at Baseline, every 24 weeks thereafter, and the Early Discontinuation/End of Treatment Visit (weight at every visit through Final Visit). For study participants enrolled prior to Protocol Amendment 9, Tanner stages assessment will be performed every 48 weeks following Protocol Amendment 8, and only for those subjects who have not reached Tanner stage V.
- Autoantibody (antinuclear antibodies [ANA] and anti-double-stranded deoxyribonucleic acid [anti-dsDNA] antibodies) concentrations will be evaluated at Baseline (testing for anti-dsDNA antibodies only if ANA is positive), Weeks 16 and 48, and at the Early Discontinuation/End of Treatment Visit.

Other efficacy and health outcomes variables are:

- PedACR30, PedACR50, PedACR70, and PedACR90 response rates at every visit except Week 16 and Final Visit as compared to Baseline (see Section 11.1 for definition).
- Change from Baseline in number of joints with active arthritis at every visit except Final Visit.
- Change from Baseline in number of joints with limitation of range of motion at every visit except Final Visit.
- Change from Baseline in Physician's Global Assessment of Disease Activity (VAS) at every visit except Final Visit.
- Change from Baseline in CHAQ at every visit except Final Visit.
- Change from Baseline in Parent's Assessment of Arthritis Pain (VAS) at every visit except Final Visit.
- Change from Baseline in Parent's Global Assessment of Overall Well-Being (VAS) at every visit except Final Visit.
- Ratio to Baseline in CRP at every visit except Final Visit.
- Change from Baseline in JADAS at every visit except Final Visit.
- Percentage of study participants with Clinically Inactive Disease (CID), as defined in Section 11.10, at every post-Baseline visit except Final Visit.
- Percentage of study participants with clinical remission on medication (CRM), as defined in Section 11.10, at every post-Baseline visit from Week 24 onwards except Final Visit.
- Time (in days) to CID.
- Time (in days) to CRM.
- Change from Baseline in DMS at every visit except Final Visit.
- Change from Baseline in FPS-R (child-reported, ages 5 to 11 years), daily during the first week of treatment; Weeks 4, 12, 16, 24, and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit. For study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8.
- Change from Baseline in JIA Pain VAS, daily during the first 7 days of the study (acute and standard versions); and at Weeks 4, 12, 16, 24, and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit (standard version) for study participants ages 12 to 17 years. For study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8.
- Change from Baseline in Fatigue Assessment Scale at every visit except Weeks 12 and 20, and Final Visit.

- Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey responses at Baseline, Week 4, and every visit thereafter except Final Visit.

5 STUDY DESIGN

5.1 Study description

This is a Phase 3, multicenter, open-label study to assess the PK, safety, and efficacy of CZP in children and adolescents with moderately to severely active polyarticular-course JIA.

Please refer to Study Schedule of Assessments in Section 5.2 for visit-specific procedures and to Section 5.3 for a schematic representation of the study.

The overall study consists of a Screening Period of up to 4 weeks (between Weeks -4 to 0 [Visits 1 and 2]) and an open-label Treatment Period which will continue until the approval of the marketing application for the polyarticular-course JIA indication in the study participant's country or region or until further notice from UCB. A Final Visit will be conducted 12 weeks after last dose of study medication.

A Screening Visit is used to initiate assessments of eligibility. Certolizumab pegol will be administered as a fixed dose based on weight throughout the study (see Table 7-1 for doses administered and Section 5.4.2 for the rationale for the different dose regimens). At Baseline (Week 0, Visit 2) eligible study participants will begin with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study. After Week 4 (Visit 5), home-based CZP administration by the study participant or parent/caregiver will be permitted between scheduled study visits.

Interim analyses were performed as described in Section 13.7. A full interim analysis will be performed after all active study participants have completed the Week 24 (Visit 10) assessments.

Pharmacokinetic data from this study that were assayed with an enzyme-linked immunosorbent assay (ELISA) technique will not be used for submission to the Food and Drug Administration (FDA) to complete the Pediatric Research Equity Act commitment, primarily due to deficiencies detected with the use of the bioanalytical assay within RA0043. All study participants enrolled following Protocol Amendment 9 will have plasma concentrations of CZP and anti-CZP antibodies analyzed using an ECLIA method that meets current regulatory standards. In addition, PK and ADA samples (for which sufficient volume is available) collected in this study prior to Protocol Amendment 9 will be analyzed with the ECLIA method. The collective ECLIA-based PK data for this study will form the basis of any future CZP modeling and simulation work.

5.1.1 Study duration per study participant

For each study participant, there will be a Screening Period of up to 4 weeks (Weeks -4 to 0). Eligible study participants will subsequently initiate open-label treatment with CZP at Baseline (Week 0, Visit 2) and be permitted to continue until the approval of the marketing application for the polyarticular-course JIA indication in the study participant's country or region, or until further notice from UCB. The Final Visit will be conducted 12 weeks after the last dose of study medication.

The end of the study is defined as the date of the last study participant's Final Visit.

First Study participant, First Visit – 1Q 2012

Planned Last Study participant, First Visit – 3Q 2021

5.1.2 Planned number of study participants and sites

Approximately 195 study participants are planned to be screened at about 55 centers in order to enroll 156 study participants in this study, as follows:

- A minimum of 10 study participants will be enrolled on the reduced CZP dose regimen in each weight range of 10 to <20kg (22 to <44lb), 20 to <40kg (44 to <88lb), and ≥40kg (≥88lb) (See Section 7.2 for the doses administered in the study and Section 5.4.2.2 for the rationale for the reduced CZP dose regimen).
- A minimum of 10 study participants will be enrolled in each age category of 2 to 5 years, 6 to 11 years, and 12 to 17 years, irrespective of the dose regimen.
- A minimum of 25 study participants will be enrolled who receive CZP as monotherapy (ie, study participants with established intolerability or inadequate response to MTX), irrespective of the dose regimen.
- A minimum of 10 study participants with ERA will be enrolled, irrespective of the dose regimen.
- The enrollment per site is limited to a maximum of 15 study participants.

Recruitment based on all protocol amendments prior to Protocol Amendment 9 is complete. Following Protocol Amendment 9, an additional 30 study participants will be enrolled on the original dose regimen with the aim to enroll at least 5 study participants in each weight range of 10 to <20kg (22 to <44lb), 20 to <40kg (44 to <88lb), and ≥40kg (≥88lb) (See Section 7.2 for the doses administered in the study and Section 5.4.2.1 for the rationale for the original CZP dose regimen).

Each of these categories is assessed independently. For instance, a 12kg, 3-year old study participant unable to tolerate MTX contributes to the enrollment goals for the 10 to <20kg (22 to <44lb) weight group, the 2- to 5-year-old age group, and the CZP as monotherapy group.

5.1.3 Anticipated regions and countries

The regions planned for participation in this study are North and South America and Russia, with possible extension to other regions.

5.2 Schedule of study assessments

Table 5-1 Schedule of study assessments

Study period	Screening	Baseline							
Week	-4 to 0[a]	0	1	2	4, 8, 12, 16, (17[u]), 20, 24	32 and every 8 weeks thereafter [z]	Unsch. Visit[b]	Early Disc/ End of Treatment	Final Visit[c]
Visit (+/-3 days)[a]	1	2	3	4	5 to 10	11 onwards			FV
Written informed consent/assent	X								
Assessment of inclusion/exclusion criteria	X	X							
Demography, JIA history, prior JIA medication, general medical and procedure history	X								
Vital signs[d]	X	X	X	X	X	X	X	X	X
Height	X[e]	X			X[f]	X[f]		X[f]	
Weight[g]	X[e]	X	X	X	X	X		X	X
Tanner stages (except growth)		X			X[f]	X[f]		X[f]	
Physical examination[h]	X	X			X	X		X	X
TB questionnaire	X	X			X[i]	X[i]		X[i]	
Hematology/biochemistry/urinalysis[j]	X[k]	X[l]			X	X		X	X
Reproductive potential and birth control	X	X			X	X		X	X
Pregnancy testing[m]	X	X			X[m]	X		X	X
C-reactive protein[j]	X	X	X	X	X	X		X	
TB screening[n] and chest x-ray[o]	X					X[n]			
PRINTO/PRCSG standard joint examination	X	X	X	X	X	X		X	
Physician's Global Assessment of Disease Activity	X	X	X	X	X	X		X	
CHAQ-parent reported	X	X	X	X	X	X		X	
Parent's Assessment of Arthritis Pain	X	X	X	X	X	X		X	
Parent's Global Assessment of Overall Well-Being	X	X	X	X	X	X		X	
Clinically Inactive Disease and clinical remission[p]			X	X	X	X		X	
Duration of morning stiffness		X	X	X	X	X		X	
JADAS		X	X	X	X	X		X	

Table 5-1 Schedule of study assessments

Study period	Screening	Baseline							
Week	-4 to 0[a]	0	1	2	4, 8, 12, 16, (17[u]), 20, 24	32 and every 8 weeks thereafter[z]	Unsch. Visit[b]	Early Disc/ End of Treatment	Final Visit[c]
Visit (+/-3 days)[a]	1	2	3	4	5 to 10	11 onwards			FV
Faces Pain Scale-Revised[q]		X			X	X		X	
Patient's Assessment of Arthritis Pain[r], acute		X							
Patient's Assessment of Arthritis Pain[r], standard		X			X[r]	X		X	
Fatigue Assessment Scale		X	X	X	X[s]	X		X	
Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey (parent/caregiver-reported)		X			X	X		X	
Concomitant medications and procedures[t]	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
IXRS contact	X	X	X	X	X	X		X	X
CZP plasma concentrations		X	X		X[u]	X[v]			
Anti-CZP antibodies		X	X		X[u]	X[v]			
Autoantibodies (ANA and anti-dsDNA antibodies)[j]		X[w]			X[x]	X[x]		X	
CZP administration[y]		X		X	X	X			

ANA=antinuclear antibody; anti-dsDNA=anti-double-stranded deoxyribonucleic acid; BCG=Bacille Calmette-Guérin; CHAQ=Childhood Health Assessment Questionnaire; CZP=certolizumab pegol; Disc=discontinuation; IGRA=interferon-gamma release assay; IXRS=interactive voice/web response system; JADAS=Juvenile Arthritis Disease Activity Score; JIA=juvenile idiopathic arthritis; PRINTO/PRCSG=Paediatric Rheumatology INternational Trials Organisation/Pediatric Rheumatology Collaborative Study Group; TB=tuberculosis; TST=tuberculin skin test; Unsch=Unscheduled

[a] Screening Visit must be completed at least 4 to 12 working days prior to the Baseline Visit, depending on regional requirements and laboratory assessments required for the study participant (please refer to Section 10.6 and the laboratory manual). For all other visits, the Visit window is ±3 days relative to Baseline.

[b] Vital signs, concomitant medications, concomitant procedures, and AEs must be assessed at every Unscheduled Visit. Other PK and safety assessments should be performed as related to nature of the visit. For Unscheduled Visits related to the dose changes, see Sections 7.2.1 and 8.6.1. For these Unscheduled Visits, the same visit window applies, ie, ±3 days.

[c] Final Visit should be performed 12 weeks after the final dose of CZP.

[d] Pulse, systolic/diastolic blood pressure, and temperature to be measured within approximately 15 minutes prior to dosing and in addition (pulse and blood

Table 5-1 Schedule of study assessments

Study period	Screening	Baseline							
Week	-4 to 0[a]	0	1	2	4, 8, 12, 16, (17[u]), 20, 24	32 and every 8 weeks thereafter[z]	Unsch. Visit[b]	Early Disc/ End of Treatment	Final Visit[c]
Visit (+/-3 days)[a]	1	2	3	4	5 to 10	11 onwards			FV

pressure only) approximately 30 minutes after dosing.

e Change in height and weight over the last 6 months and over the last year will be collected via parent-/self-report, if not available from medical records.

f Height and Tanner stages to be measured at Week 24 and 48, every 24 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, Tanner stages assessment will be performed every 48 weeks following Protocol Amendment 8, and only for those subjects who have not reached Tanner stage V) and at Early Discontinuation/End of Treatment.

g From Week 2 onwards, weight measurements will be used to readjust the CZP dose as needed according to Table 7-1.

h Physical examination findings (except joint examination) are recorded in the CRF only at Screening. Subsequent physical examinations are to be recorded in the source documentation and clinically significant findings recorded as AEs.

i TB questionnaire to be completed at Weeks 12 and 24 and every 16 weeks thereafter, and Early Discontinuation/End of Treatment. If the Investigator suspects latent TB or active TB, TB testing and/or a chest x-ray should be performed as outlined in Section 10.7.9.

j Hematology/biochemistry/urinalysis will be performed by a central laboratory, except urine dipsticks, which will be done locally at the site. Study participants do not have to be fasting.

k At Screening, laboratory testing includes testing for hepatitis B core antibody, hepatitis B surface antibody, hepatitis B surface antigen, hepatitis C virus antibody, and HIV 1/2. Study participants with a positive hepatitis B virus test will not be allowed in the study (except for anti-hepatitis B surface positive only, in case study participant is immune due to well-documented hepatitis B vaccination or isolated false-positive anti-hepatitis B core test confirmed with a confirmatory test such as hepatitis B virus deoxyribonucleic acid [DNA]). A positive hepatitis C antibody test will be confirmed by a confirmatory test (such as hepatitis C virus ribonucleic acid [RNA]) and those with a positive confirmatory test will not be allowed in the study.

l At Baseline, hematology/chemistry/urinalysis only need to be done if in the Investigator's opinion there is a change in the study participant's status compared to the Screening Visit.

m Pregnancy testing for postmenarcheal female study participants. Serum testing by a central laboratory at Screening and urine testing locally at the site at Baseline, Weeks 8, 16, 24, and every visit thereafter.

n TB screening: Interferon-gamma release assay (IGRA) testing (QuantiFERON®) is required to be performed by the central lab for all study participants from 5 to 17 years of age. TST and IGRA testing at Screening is mandatory for study participants less than 5 years of age in this study unless written documentation of BCG vaccination is available (refer to Section 6.2 [exclusion criterion 11] and Section 10.7.9). Following implementation of Protocol Amendment 7, IGRA testing (QuantiFERON) should be done once a year (approximately every 48 weeks) for all study participants.

o Chest radiographic imaging is done at Screening and results must be available at Baseline before first drug administration, unless a chest x-ray or CT is available within 2 months prior to Screening.

p Clinical remission on medication will be assessed at every post-Baseline visit from Week 24 onwards only.

Table 5-1 Schedule of study assessments

Study period	Screening	Baseline							
Week	-4 to 0[a]	0	1	2	4, 8, 12, 16, (17[u]), 20, 24	32 and every 8 weeks thereafter[z]	Unsch. Visit[b]	Early Disc/ End of Treatment	Final Visit[c]
Visit (+/-3 days)[a]	1	2	3	4	5 to 10	11 onwards			FV

[q] For study participants ages 5 to 11 years. Daily assessment during the first week (Baseline and Day 1 to Day 7, to be collected at Week 1). In addition, to be completed at Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) through the End of Treatment/Early Discontinuation Visit.

[r] For study participants ages 12 to 17 years. Daily assessment of acute VAS version during the first week (at Baseline and Day 1 to Day 7, to be collected at Week 1). In addition, standard VAS version to be completed at Baseline, Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) through the End of Treatment/Early Discontinuation Visit for study participants ages 12 to 17 years.

[s] Fatigue Assessment Scale performed at Weeks 4, 8, 16, and 24.

[t] Concomitant procedures are collected starting at Baseline.

[u] CZP plasma concentration and anti-CZP antibodies to be measured at Weeks 4, 12, 16, and 24. A postdose CZP plasma sample will be collected at approximately 5 to 7 days following the Week 16 Visit (ie, requires an additional clinic site visit for blood collection at Week 17). Samples for CZP plasma concentration and anti-CZP antibodies will be collected as separate samples.

[v] CZP plasma concentration and anti-CZP antibodies to be measured at Weeks 32, 40, 48, and every 24 weeks thereafter for study participants enrolled following Protocol Amendment 9. For study participants enrolled prior to Protocol Amendment 9, samples for CZP plasma concentration and anti-CZP antibodies will no longer be collected. Samples for CZP plasma concentration and anti-CZP antibodies will be collected as separate samples.

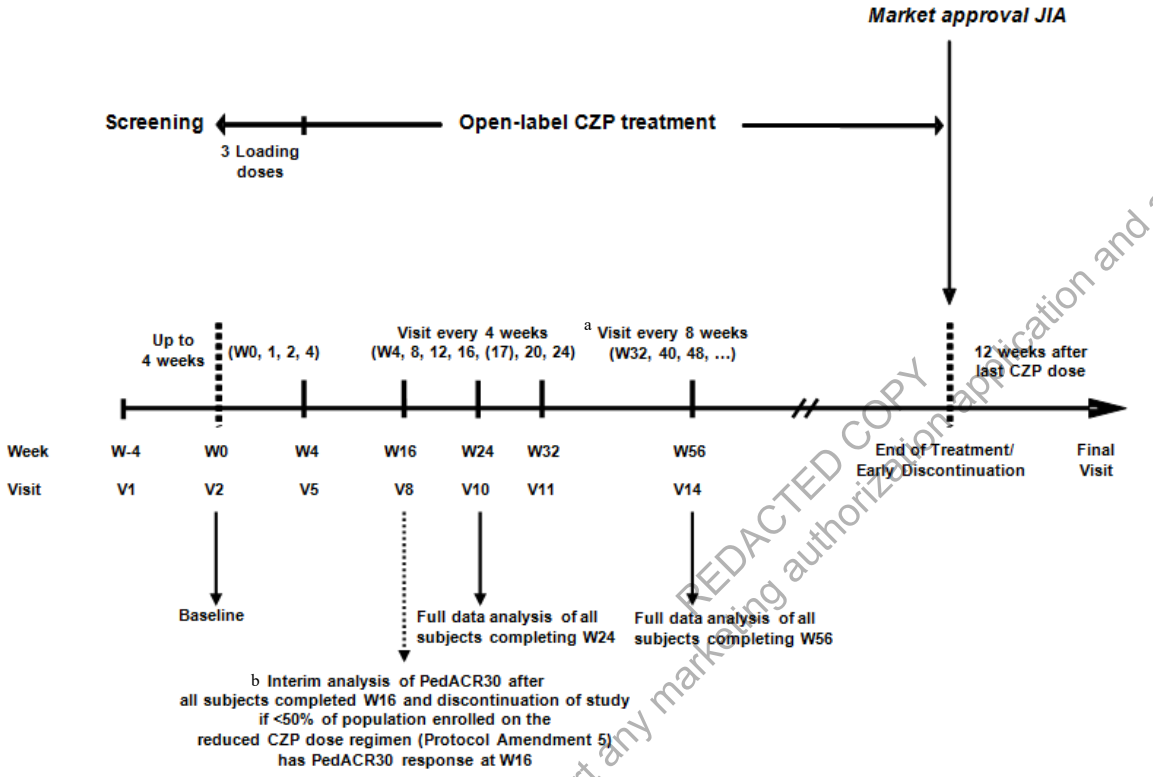
[w] At Baseline, testing for anti-dsDNA antibodies will only be done if ANA is positive.

[x] ANA and anti-dsDNA antibodies performed at Week 16 and Week 48.

[y] After Week 4 (Visit 5) study participants/caregivers may administer CZP Q2W (or Q4W for the lowest weight group) at home between scheduled study visits. See Section 7.2 regarding training and option for continued site administration.

[z] For study participants enrolled prior to Protocol Amendment 9, on-site CZP administration, safety sampling, and efficacy assessment frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8, provided that compliance is maintained with the CZP dosing schedule using at-home administration. The option to come to the site for CZP administration between scheduled visits is available as needed.

5.3 Schematic diagram



[a] Following Week 32, visits will be every 8 weeks. For study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8.
[b] The futility analysis of PedACR30 after all study participants on the reduced CZP dose completed Week 16 has already been completed. A further futility analysis will not be performed using the additional study participants that will be enrolled on the original CZP dose regimen following the implementation of Protocol Amendment 9.

5.4 Rationale for study design and selection of dose

5.4.1 Study design

Following the US approval of CZP for the treatment of moderately to severely active RA in adults, the FDA has required a postmarketing pediatric study. The following open-label study has been accepted to fulfill the FDA postmarketing requirement to investigate CZP PK, dosing, safety, and immunogenicity in the pediatric population (2 to 17 years old, inclusive) with JIA.

Conducting placebo-controlled studies in pediatric populations requires special consideration. These include ethical concerns associated with denying active treatment to a population of patients that cannot make their own fully-informed choices about healthcare, the enrollment difficulties commonly encountered for placebo-controlled pediatric studies, and the limited size of the patient population from which to recruit. Studies in JIA are no exception for these considerations.

Currently, 2 TNF-antagonists (ETN and ADA) have been approved in the USA and Europe for the treatment of JIA. For both TNF-antagonists, similarities between the adult RA and the JIA population were shown in the placebo-controlled clinical studies with respect to efficacy, safety and dosing. Through extensive interactions between the FDA and external experts, culminating in a collaborative workshop in October 2019 entitled “Accelerating Drug Development for polyarticular Juvenile Idiopathic Arthritis (pJIA)”, a therapeutic bridging approach from RA to pJIA was strongly supported for TNF-α inhibitors based on the relationship between RA and pJIA and the extensive knowledge of TNF-α inhibitors as therapeutic agents in these two populations. This approach (based on "Pharmacokinetic (PK) matching") directs that the therapeutic effect of TNF-α inhibitors (such as CZP) in pJIA patients can be expected if the pediatric systemic exposure for the drug is within the therapeutic range for adult RA patients.

Study RA0043 is being undertaken in support of the pJIA Pediatric Research Equity Act (PREA) requirement for CZP. The pJIA development program for CZP will be based on PK data generated with the newly validated MSD ECLIA method for pediatric study participants in (Section 7.2 and Section 5.4.2). To enable this approach, an additional 30 study participants will be enrolled in RA0043 following Protocol Amendment 9 at the original CZP dosing regimen.

Central to application of this approach is the existence of a reference systemic exposure (PK) range which is associated with therapeutic benefit of the drug in adult RA population. A supporting adult reference PK dataset for "PK matching" in the pJIA program will also need to be based on data generated with the ECLIA method. Accordingly, a separate study is being undertaken in order to generate ECLIA-based CZP PK data for CZP in adults with RA.

5.4.2 Dose selection

The original minimum and maximum loading doses in the study were CZP 100mg Q2W and CZP 400mg Q2W, respectively, and the original minimum and maximum maintenance doses were CZP 50mg Q2W and CZP 200mg Q2W, respectively (see Section 5.4.2.1 for the rationale for the original CZP dose regimen). Based on an interim PopPK analysis of RA0043 data, the minimum and maximum loading doses in the study were adjusted to CZP 50mg

Q2W and CZP 200mg Q2W, respectively, and the minimum and maximum maintenance doses were adjusted to CZP 50mg Q4W and CZP 100mg Q2W, respectively, following implementation of Protocol Amendments 4 and 5 (see Section 5.4.2.2 for the rationale for the reduced CZP dose regimen).

However, it was later determined that there were deficiencies detected with the use of the bioanalytical assay within RA0043, which rendered the PK data for the PopPK analysis and simulations that informed the dose reduction in Protocol Amendment 4 and 5 unusable from a regulatory standpoint. Accordingly, PK samples were no longer collected for study participants on the reduced CZP dose regimen following implementation of Protocol Amendment 8.

An ECLIA method, for which selectivity had previously been assessed in the RA matrix, has now been validated to meet the standards set in the regulatory guidance for analytical procedures and methods validations for drugs and biologics (FDA, Guidance for Industry – Bioanalytical Method Validation, 2018). The ECLIA assay consists of a homogeneous bridging immunoassay on the MSD platform.

Based on 24-week interim results from RA0043 (Section 13.7), both the original and reduced dose regimens showed safety profiles similar to the approved CZP dose regimen in the adult RA population. The overall clinical response in the study (taking both dose regimens into account) was PedACR30 and PedACR50 responses of 77.3% and 67.5%, respectively at Week 12. The response from the original dose regimen was 75.6% for PedACR30 and 64.1% for PedACR50. PedACR50 response demonstrates a highly clinically relevant decrease in disease activity.

Therefore, in order to adequately assess the exposure levels and clinical experience of CZP in pJIA at both the reduced and original CZP dose regimens and also adequately support the safety assessment of the original CZP dosing regimen, as more of the safety data collected in the study to date has been on the reduced dose, 30 additional study participants will be enrolled on the original CZP dose regimen following Protocol Amendment 9. All study participants enrolled following Protocol Amendment 9 will have plasma concentrations of CZP and anti-CZP antibodies analyzed using the ECLIA method. In addition, PK and ADA samples (for which sufficient volume is available) collected in this study prior to Protocol Amendment 9 will be analyzed with the ECLIA method. The collective ECLIA-based PK data for this study will form the basis of any future CZP modeling and simulation work.

5.4.2.1 Original CZP dose regimen

The recommended dosing regimen for CZP in adult study participants with moderate to severe RA is CZP 400mg sc at Weeks 0, 2, and 4 followed by CZP 200mg Q2W thereafter. This dose regimen was evaluated for safety and efficacy in 2 double-blind, placebo-controlled, Phase 3 clinical studies (C87027 and C87050) and supported by population PK/pharmacodynamic (PD) modeling (C87079). The PK/PD model estimated EC_{50} C_{avg} plasma concentration (the CZP concentration that produces one-half of the maximum effect for ACR20 response) to be 16.8µg/mL (95% confidence interval [CI] = 10.2 to 23.4).

Population PK analysis on data from adult study participants with RA (C87068) showed that there was a less than proportional inverse relationship between body weight and PK. The

adult PopPK model was used to predict the effect of extreme body weights on PK exposure in typical adult study participants with RA at steady state using the recommended dose regimen as shown in Table 5-2.

Table 5-2 PK estimates of CZP exposure in adult study participants with RA based on population PK modeling

Body weight (kg)	C_{max} (µg/mL)	C_{trough} (µg/mL)	AUC (µg.day/mL)
40	53	34	616
70	41	22	457
120	33	14	334

AUC=area under the curve; C_{max}=maximum serum concentration; C_{trough}=trough serum concentration; CZP=certolizumab pegol; PK=pharmacokinetic; RA=rheumatoid arthritis

The therapeutic plasma concentration of CZP in children and adolescents with JIA was expected to be similar to that required for the adult population with RA. In adults with RA, effective plasma concentrations are achieved with doses of CZP 400mg at Weeks 0, 2, and 4, followed by CZP 200mg Q2W thereafter. The intention in RA0043 is to study the equivalent dose regimen in children and adolescents with JIA. Initial predictions, based on allometric scaling of PK data from adults, suggested that this could be achieved by reducing the dose of CZP for pediatric study participants with body weights between 20 to <40kg (44 to <88lb) to CZP 200mg at Weeks 0, 2, and 4 followed by CZP 100mg Q2W (ie, 50% of the recommended adult dose), and by reducing the dose further to 25% of the adult dose for study participants with body weights 10 to <20kg (22 to <44lb) (ie, CZP 100mg at Weeks 0, 2, and 4 followed by CZP 50mg Q2W).

The original choice of dose and the weight-based dose-adjustment algorithm was supported by simulations of the PK exposure and response rates in children using the PopPK model and PK/PD exposure response model developed in adult RA study participants, corrected for pediatric demographics (C87079 addendum 08 Oct 2008). Results of these simulations showed that all age groups exhibit similar exposures (C_{max} and AUC_T) to those of adults over the Week 14 to Week 16 dosing interval, with the pediatric/adult ratio of the median predicted values of PK parameters ranging from 1.03 to 1.19 for C_{max} and from 0.97 to 1.18 for AUC_T. The similarities in exposures were reflected in the probability of ACR20 response, which are similar for all age groups at Week 16 (pediatric/adult ratio of the median predicted values ranging from 1.08 to 1.10). These simulations were performed upon the assumption that disease progression and response rate for a given exposure are similar in children and adults.

The original CZP dose regimen is the regimen that will be used for study participants enrolled following Protocol Amendment 9.

5.4.2.2 Reduced CZP dose regimen

Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future analyses indicate that plasma concentrations were outside of the exposure range of those observed in previous studies with adults, the dosing algorithm could have been changed

via a protocol amendment, and if necessary, additional interim analyses including PopPK, could have been performed.

Results of an interim PopPK analysis conducted following Protocol Amendment 3 (in Jun 2013) suggested that while observed CZP plasma concentrations remained in the adult range, they were at the upper end of the distribution. Simulations predicted that for some study participants in RA0043 receiving the originally determined loading doses up to Week 4 (Visit 5), plasma concentrations were likely to exceed the range previously seen in adult study participants receiving CZP 400mg Q2W. Furthermore, plasma concentrations of study participants receiving the originally determined maintenance dose after Week 4 (Visit 5) were predicted to exceed the concentration range observed in adults receiving CZP 200mg Q2W. Based on these findings, the dosing regimen was changed with Protocol Amendments 4 and 5, and the doses to be administered were reduced by 50% for all weight groups. This dose change was intended to achieve plasma concentrations that were similar to the effective concentrations observed in previous studies in adult study participants with RA.

Subsequently, the maintenance doses in this study were reduced with Protocol Amendment 4 so that study participants with body weights between 20 and <40kg (44 to <88lb) received CZP 50mg Q2W, and study participants with body weights of ≥40kg (≥88lb) received CZP 100mg Q2W (see Table 7-1). The optimal maintenance dose estimated in the PopPK model for the lowest weight group was CZP 25mg Q2W, however, the lowest available dose size is CZP 50mg. Thus, study participants with body weights of 10 to <20kg (22 to <44lb) received CZP 50mg Q4W to achieve this 50% reduction. In addition, with Protocol Amendment 5, the loading dose in the study was reduced by 50% for newly enrolled study participants, so that study participants with body weights of 10 to <20kg (22 to <44lb) received CZP 50mg at Weeks 0, 2, and 4, study participants with body weights between 20 to <40kg (44 to <88lb) received CZP 100mg at Weeks 0, 2, and 4, and study participants with body weights ≥40kg (≥88lb) will receive CZP 200mg at Weeks 0, 2, and 4.

The rationale behind selecting the equivalent of the adult therapeutic dose was based on the following:

- There is no metabolic rationale to expect a difference in the PK/PD of CZP in a younger population, particularly as there is no involvement of cytochrome P450.
- Evaluation of a previous anti-TNF antibody (CDP571, a whole antibody) in a pediatric population (administered iv) confirmed that the PK and safety were similar to that of an adult population.
- Doses in excess of CZP 400mg (up to CZP 800mg) have been administered to healthy adult study participants and study participants with RA without any dose-limiting toxicities being identified.
- A conservative approach to dose reduction was chosen because the body weight of pediatric study participants may be influenced largely by frame size while the range of body weight of adults may be more influenced by percent body fat.

However, it was later determined that there were deficiencies detected with the use of the bioanalytical assay within RA0043, which rendered the PK data for the PopPK analysis and

simulations that informed the dose reduction in Protocol Amendment 4 and 5 unusable from a regulatory standpoint. Study participants enrolled prior to the implementation of Protocol Amendment 9 can remain on the reduced CZP dose or may be switched to the original CZP dose at the discretion of the Investigator and in consultation with the medical monitor. Additional dose changes are not allowed (Section 7.2.1).

6 SELECTION AND WITHDRAWAL OF STUDY PARTICIPANTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the study participant or by the parent(s) or legal representative. The Consent form or a specific Assent form, where required, will be signed and dated by minors.
2. Study participant/legal representative/parent is considered reliable and capable of adhering to the protocol, visit schedule or medication intake according to the judgment of the Investigator.
3. Study participant must be able and willing to comply with the requirements of the study.
4. Study participant is 2 to 17 years of age (inclusive) at Baseline (Visit 2).
5. Study participants must weigh ≥10kg (22lb) at Baseline (Visit 2).
6. Study participants must have had onset of signs and symptoms consistent with a diagnosis of JIA (according to the International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis, 2001) and initiation of JIA treatment for at least 6 months prior to Baseline (Visit 2). Eligible JIA categories include: polyarthritis rheumatoid factor-positive, polyarthritis rheumatoid factor-negative, extended oligoarthritis, juvenile psoriatic arthritis, and ERA.
7. Study participants must have active polyarticular-course disease, defined as ≥5 joints with active arthritis at Screening and at Baseline.
8. Study participants must have had an inadequate response to, or intolerance to, at least 1 DMARD (nonbiologic or biologic). For example, study participant had prior inadequate response to MTX (based on the Investigator's clinical judgment).
9. If the study participant is using MTX, then the study participant must have been on MTX for a minimum of 3 months at Screening. In addition, the dose must have been stable for at least 1 month before Screening at ≥10 to ≤15mg/m^2 per week. If the study participant is not using MTX, then the treatment must have been previously withdrawn for documented reasons of intolerability or inadequate response.
10. If the study participant is using oral corticosteroid therapy, the dose must have been stable for at least 7 days prior to the Baseline arthritis assessment at a maximum dose of 10mg or 0.2mg/kg prednisone (or equivalent) per day, whichever is the smaller dose.

6.2 Exclusion criteria

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

1. Study participant has previously been exposed to more than 2 biologic agents.
2. Study participant previously failed to respond to treatment with more than one tumor necrosis factor alpha (TNFα) antagonist drug. Lack of response to treatment is defined as no clinical disease improvement within the first 12 weeks of treatment. (Study participants who demonstrated clinical response within 12 weeks of treatment and subsequently lost response after 12 weeks of treatment are eligible.)
3. Study participant is currently receiving or has received any experimental (biological or non-biological) therapy (within or outside a clinical study) in the 3 months or 5 half-lives prior to Baseline (Visit 2), whichever is longer.
4. Study participant had previous treatment with a biological therapy for JIA that resulted in a severe hypersensitivity reaction or an anaphylactic reaction.
5. Study participant previously participated in this study or has previously been treated with CZP (whether in a study or not).
6. Study participant has received any prohibited medication as detailed in Table 6-1.

Table 6-1 Prohibited medications at entry (Baseline)

Drug class	Prohibited dose	Exclusion criteria
Oral corticosteroids	Any dose greater than 10mg or 0.2mg/kg prednisone (or equivalent) per day, whichever is the smaller dose	Any change in dose in the 7 days prior to the Baseline arthritis assessment.
im/iv/ia corticosteroids	Any dose	Use within 28 days prior to the Baseline arthritis assessment.
Non-biologic DMARDs (eg, sulfasalazine, hydroxychloroquine, cyclosporine)	Any dose For MTX, any dose <10 or >15mg/m^2 per week	Use within 28 days prior to the Baseline arthritis assessment. For MTX, any change in dose in the 1 month prior to Screening. Use of cyclosporine within 7 days prior to the Baseline arthritis assessment. Use of leflunomide within 6 months prior to the Baseline arthritis assessment if a cholestyramine washout is not performed (and 28 days prior if performed).
Biologic DMARDs	Any dose	Prior or current exposure to more than 2 biologic DMARDs and/or primary failure (defined as a complete lack of response) to more than 1 TNF inhibitor. Use of anakinra or rilonacept within 7 days prior to the Baseline arthritis assessment. Use of etanercept within 28 days prior to the Baseline arthritis assessment. Use of adalimumab within 56 days prior to the Baseline arthritis assessment. Use of infliximab or abatacept within 60 days prior to the Baseline arthritis assessment. Use of rituximab within 180 days prior to the Baseline arthritis assessment. Use of any other biological response modifier therapy (eg, tocilizumab, canakinumab) within 90 days or 5 half-lives prior to the Baseline arthritis assessment, whichever is longer. (All aforementioned drugs are prohibited during the study.)

DMARDs=disease-modifying antirheumatic drugs; ia=intra-articular; im=intramuscular; iv=intravenous; JIA=juvenile idiopathic arthritis; TNF=tumor neucrosis factor

7. Study participant has a history of systemic JIA, with or without systemic features.
8. Study participant has a secondary, noninflammatory type of rheumatic disease or of joint pains (eg, fibromyalgia) that in the Investigator's opinion is symptomatic enough to interfere with evaluation of the effect of study medication.
9. Study participant has other inflammatory arthritis (eg, systemic lupus erythematosus, inflammatory bowel disease-related).
10. Study participant has active uveitis or a history of active uveitis within the preceding 6 months.
11. Participant has:
    a. Known active TB disease
    b. History of active TB involving any organ system
    c. History of or current latent tuberculosis infection (LTBI)
    d. High risk of exposure to TB infection
    e. Current nontuberculous mycobacterial (NTMB) infection or history of NTMB infection. For further information relating to definitions of known active TB, past history of TB, LTBI, high risk of acquiring TB infection and NTMB infection, refer to Section 10.7.9 (Assessment and management of TB and TB risk factors).
12. Study participant has a current sign or symptom which may indicate infection (eg, fever, cough), a history of chronic or recurrent infections within the same organ system (more than 3 episodes requiring antibiotics/antivirals during the 12 months prior to Screening [Visit 1]), had a recent (within the 6 months prior to Screening [Visit 1]) serious or life-threatening infection (including herpes zoster), or is at a high risk of infection in the Investigator's opinion (eg, study participants with leg ulcers, indwelling urinary catheter, and persistent or recurrent chest infections or permanently bed-ridden or wheelchair bound).
13. Study participant has a history of or current hepatitis B or C virus or HIV 1/2 or has any of the following laboratory abnormalities during the Screening Period:
    a. Hepatitis B surface (HBs) antigen, hepatitis B core (HBc) antibody (except for isolated, false-positive anti-HBc confirmed with a confirmatory test such as hepatitis B virus [HBV]-deoxyribonucleic acid [DNA] [refer to Table 5-1 footnote k and Section 10.6 (Clinical Laboratory Tests) table footnote c]): Positive to any of these
    b. Hepatitis C virus (HCV) positive: defined as hepatitis C antibody (anti-HCV Ab) positive confirmed via a confirmatory test (for example, HCV polymerase chain reaction)
    c. HIV antigen or antibody: Positive to either test
14. Study participant has received any live, including attenuated, vaccination within 8 weeks prior to Baseline (Visit 2) and/or is scheduled for live vaccination during the course of study participation. Non-live vaccinations are permitted at any time prior to and during the study.

15. Study participant has a history of chronic alcohol or drug abuse based on the Investigator's clinical judgment within the last 1 year.
16. Study participant is breast-feeding, pregnant or plans to become pregnant during the study or within 12 weeks following the last dose of study medication (or longer if required by local regulations). Female study participants of childbearing potential (ie, postmenarcheal) must have a negative result at Screening and Baseline (Visits 1 and 2) pregnancy tests to be eligible for study entry.
17. Study participant is a sexually active female of childbearing potential (ie, postmenarcheal) and is not practicing or will not agree to practice an effective means of birth control. For postmenarcheal female study participants not currently sexually active, the study participant and parent or legal representative should agree that the study participant will employ an effective means of birth control consistently and correctly should the study participant become sexually active. Effective methods of birth control are: oral/parenteral/implantable hormonal contraceptives (stable at least 2 months prior to Screening (Visit 1) if initiated prior to entering the study) or a combination of barrier and spermicide. Study participants must agree to use effective contraception during the study and for 12 weeks after their last dose of study medication (or longer if required by local regulations). Male study participants who are sexually active must agree to ensure they or their female partner(s) uses adequate contraception during the study and for 12 weeks after the study participant receives their last dose of study medication (or longer if required by local regulations). (Sexually active means engaging in sexual intercourse, regardless of frequency).
18. Study participant has a history of an adverse reaction to PEG.
19. Study participant has a history of a lymphoproliferative disorder including lymphoma or signs and symptoms at any time suggestive of lymphoproliferative disease.
20. Study participant has a concurrent malignancy, or a history of any malignancy.
21. Study participant has a current or recent history (within 6 months prior to Screening [Visit 1]) of severe, progressive, and/or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease including blood dyscrasia (eg, pancytopenia, aplastic anemia), demyelinating disease (eg, multiple sclerosis, myelitis, optic neuritis).
22. Study participant has any other medical or psychiatric condition that, in the opinion of the Investigator or Sponsor, could jeopardize or would compromise the study participant's ability to participate in the study or which otherwise make the study participant unsuitable for inclusion in the study.
23. Study participant has any clinically significant laboratory abnormalities which, in the Investigator's judgment, would make the study participant unsuitable for inclusion in the study, with specific exclusion of study participants with values of: liver function tests that are >2×upper limit of normal (ULN), serum creatinine that are >1.5 ×ULN, and white blood cells that are $<3.0x10^9$/L or 3000/mm^3.
24. Study participant is wheelchair-bound at the time of enrollment.

25. Study participant with a history of or active systemic/respiratory infection due to fungal, parasitic, or mycotic pathogens including but not limited to histoplasmosis, coccidiosis, paracoccidiosis, pneumocystis, blastomyces, and aspergillus.

    Radiographic evidence suggestive of any of these infections is sufficient grounds for exclusion.

6.3 Retesting and rescreening

Retesting of laboratory assessments within the Screening Period is allowed as per the following:

- Study participants with isolated exclusionary laboratory assessments at Screening may have this laboratory assessment repeated once if, in the Investigator's opinion, the value is not reflective of the study participant's previous clinical and laboratory pattern. Retesting must be completed within the stated Screening Period. If the repeat values are within the acceptable ranges of the study and the study participant remains eligible during the Baseline Visit (Week 0), the study participant may be dosed.

Rescreening is only allowed after consultation with the Medical Monitor as per the following:

- Study participants who failed Screening (eg, due to transient out-of-range safety laboratory values or in the Investigator's judgment mild acute illness, eg, a cold) may be rescreened after complete recovery of the mild acute illness and/or normalization of the out-of-range safety laboratory values.
- Study participants who fulfilled all eligibility criteria but were registered as Screen failures due to suspension of enrollment as of 17 Jul 2013 are allowed to be rescreened.
- Rescreening might be allowed more than once but not in case of repeated occurrence of the same illness. All Screening assessments must be repeated as applicable in case of Rescreening. The maximum duration of the Rescreening Period is 28 days or 4 weeks. Rescreening must only be scheduled after an appropriate time period after the initial Screening Visit allowing for repetition of blood collection (depending on local requirements for maximum blood volumes; depending on study participant weight).
- All study participants who failed to be enrolled within the Screening Period of 28 days must be registered as Screen Failure in the interactive voice/web response system (IXRS). Study participants approved to be rescreened must be registered with a new study participant number.

6.4 Liver Chemistry Stopping Criteria

Participants with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should be discontinued. The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Participants with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Participants with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, and eosinophilia (ie, >5%).

The PDILI criterion below allows participants to continue on IMP at the discretion of the Investigator:

- Participants with ALT or AST ≥3xULN (and ≥2x baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 17.10. If participants are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on participants in the case of IMP discontinuation to complete the final evaluation. Participants with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

6.5 Withdrawal criteria

Study participants are free to withdraw from the study at any time, without prejudice to their continued care. Where possible, study participants discontinuing study medication should be encouraged to remain in the study.

A study participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the study participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a study participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Study participants should be withdrawn from the study if any of the following events occur:

1. Study participant or legal representative withdraws his/her consent.
2. The sponsor or a regulatory agency requests withdrawal of the study participant.

Study participants must be permanently discontinued from study medication (but not necessarily from the study) if any of the following occurs:

1. Study participant/caregiver is noncompliant with the study procedures or medications in the opinion of the Investigator or Sponsor.
2. A study participant considered as having either a suspected new LTBI or who develops active TB or NTMB infection during the study (including but not limited to, conversion demonstrated by interferon-gamma release assay [IGRA] or other diagnostic means) must be immediately discontinued from IMP (refer to Section 10.7.9.8 for further details).
   a) The study participant must be permanently withdrawn from the study if further examinations result in a diagnosis of active TB, NTMB infection, or if the study participant is diagnosed with LTBI. An Early Discontinuation visit must be scheduled as soon as possible, but not later than the next regular visit.

   Any confirmed diagnosis or suspicion of a latent or active TB infection is a reportable event. Either type of infection must be reported as an adverse event of special interest (AESI) and must be captured on an AE report form, ticking the appropriate AESI and, if applicable, serious adverse event (SAE) field(s) on the form to clearly indicate the level of seriousness. A UCB TB follow-up form also must be completed. Confirmed active TB is an SAE and must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirements until such time as the TB infection resolves.
3. Study participant is found to be persistently noncompliant (missing 2 or more consecutive scheduled CZP doses or missing 3 or more doses over a 12-month period), the Sponsor in conjunction with the Investigator will make a decision as to whether the study participant should be withdrawn from the study (see Section 7.7).
   This rule does not apply when CZP is discontinued if the study participant is in CRM or if CZP is temporarily discontinued due to an AE. In the case of temporary discontinuation due to an AE, the Sponsor in conjunction with the Investigator will make a decision as to whether the study participant should be withdrawn from the study.
4. Study participant takes prohibited concomitant medications as defined in this protocol (see Section 7.8.3).

Study participants may be discontinued from study medication (but not necessarily from the study) if any of the following occurs, but may be restarted after consultation with the Medical Monitor:

1. Study participant develops an illness that would interfere with continued participation (eg, malignancies).
2. If there is a positive pregnancy test, study medication will be held. If there is confirmed pregnancy, study medication must be discontinued until end of the pregnancy. In case the study participant intends to breastfeed after a pregnancy study medication must be further discontinued until end of breastfeeding.

Investigators should attempt to obtain information on study participants, in the case of withdrawal or discontinuation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the study participant, must be recorded in the source documents. For study participants considered as lost to follow-up the Investigator should make an effort (at least 1 phone call and 1 written message to the study participant), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents) to complete the final evaluation. The CRF must document the primary reason for withdrawal or discontinuation.

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

7 STUDY TREATMENTS

7.1 Description of IMP

Supplies of CZP will be provided by UCB as a CZP 200mg/mL solution for single sc injection, in a single use PFS for sc injection (administered in accordance with Table 7-1). Each PFS contains an extractable volume of 0.25mL, 0.5mL, or 1mL of CZP solution.

The IMP will be supplied under the responsibility of UCB. The frequency at which the IMP will be supplied to each individual center will be adapted based on the recruitment capacity of that center, availability, and expiry date of the IMP. Study medication supplies will be managed by the IXRS in order to ensure all sites have sufficient quantities of study medication available.

7.2 Treatments to be administered

Throughout the study, CZP dosing is fixed dose based on weight and given Q2W, with the exception of the lowest weight group on the reduced CZP regimen who will receive the maintenance dose Q4W. The loading dose, maintenance dose, and range of exposures in each weight category for both the original and reduced CZP regimens are presented in Table 7-1. Study participants start with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study. After Week 4 (Visit 5), home-based CZP administration by the study participant or parent/caregiver will be permitted between scheduled study visits.

A study participant's dosing category will only be changed after the confirmation of a weight change by the Investigator **at a scheduled clinic visit.**

The study participant will receive the dose of the next weight category once their weight crosses the 40kg/88lb boundary or crosses the 20kg/44lb boundary at a scheduled clinic visit. The study participant will continue on the dose of the new weight category regardless of potential decrease of the weight below the boundary. In case of significant weight fluctuations the Investigator should contact the Medical Monitor to discuss and confirm potential change in dosing if medically advised or discontinuation of treatment (eg, if related to AE).

The injection should be administered at either the lateral abdominal wall or upper outer thigh. Treatment of the injection site with an anesthetic cream prior to dosing is permitted.

Table 7-1 Dosing administration of CZP[a]

Weight range	Loading dose – Weeks 0, 2, and 4 (mg/kg dose range) IMP Description	Maintenance – Week 6 and onwards (mg/kg dose range) IMP Description
Original CZP regimen		
10 to <20kg (22 to <44lb)	100mg Q2W (5-10mg/kg) 1 x 0.5mL inj	50mg Q2W (2.5-5mg/kg) 1 x 0.25 mL inj
20 to <40kg (44 to <88lb)	200mg Q2W (5-10mg/kg) 1 x 1mL inj	100mg Q2W (2.5-5mg/kg) 1 x 0.5mL inj
≥40kg (≥88lb)	400mg Q2W (<10mg/kg) 2 x 1mL inj	200mg Q2W (<5mg/kg) 1 x 1mL inj
Reduced CZP regimen		
10 to <20kg (22 to <44lb)	50mg Q2W (2.5-5mg/kg) 1 x 0.25mL inj	50mg Q4W (2.5-5mg/kg) 1 x 0.25mL inj
20 to <40kg (44 to <88lb)	100mg Q2W (2.5-5mg/kg) 1 x 0.5mL inj	50mg Q2W (1.25-2.5mg/kg) 1 x 0.25mL inj
≥40kg (≥88lb)	200mg Q2W (<5mg/kg) 1 x 1mL inj	100mg Q2W (<2.5mg/kg) 1 x 0.5mL inj

CZP=certolizumab pegol; inj=injection; Q2W=every 2 weeks; Q4W=every 4 weeks

Note: A study participant should change dosing category during the course of the study if their weight crosses the 40kg/88lb boundary or crosses the 20kg/44lb boundary.

[a] Note that the original CZP regimen describes the dosing administration of CZP prior to the implementation of Protocol Amendments 4 and 5 and for study participants enrolled following the implementation of Protocol Amendment 9. The reduced CZP regimen describes the dosing administration of CZP after implementation of Protocol Amendments 4 and 5. Refer to Section 7.2.1 for the procedure to be taken for study participants who are undergoing a dose change.

Site staff will administer the study participant's injection at Week 0 to demonstrate the correct injection technique. At Weeks 2 and 4, study participants/caregivers may administer the study medication under the supervision of the site staff to ensure that the study medication is being properly and safely injected. Once study participants/caregivers have been trained, the study medication may be administered at home. Prior to CZP administration at home, study participants/caregivers will be trained by the site staff and provided written instructions on the fixed dose for injection and the correct sc injection technique including 0.25mL, 0.5mL, and 1mL injections, as appropriate. If administered at home, the study participant/caregiver is requested to document the container number, date, and time point of

administration of study medication and return this documentation together with any used/unused or partially used containers at the next scheduled clinic visit. Study participants who are unable to self-administer the study treatment or those without a family member/friend/caregiver who can help, will not be withdrawn from the study but may continue to visit the site for study treatment administration between regular scheduled visits. In addition, if needed, home dosing can be performed by qualified health care professionals according to the written instructions for the correct sc injection technique provided by the site staff. Study participants will have the option to either switch to home-based CZP injection or switch back to administration at the study site at anytime during the study.

The method of injection (ie, qualified site personnel-injection at study site; injection by the study participant/caregiver or qualified health care professional at the study site or at home) and the site of injection (abdomen, thigh) will be recorded in the CRF at each visit.

Study participants achieving clinical remission on medication (CRM), ie, after 6 months of continuous CID, may discontinue CZP treatment at the Investigator's discretion following consultation with the Sponsor to confirm remission status. Study participants who have discontinued CZP due to achieving CRM will be allowed to remain in the study and continue with scheduled study visits. Study participants not maintaining persistent CID following achievement of CRM will be allowed to resume CZP treatment at any time at the Investigator's discretion and consultation with the Sponsor. If a study participant is on concomitant MTX treatment, the Investigator may decide to decrease and ultimately discontinue the MTX dose after complete discontinuation of CZP. Study participants not maintaining persistent CID following achievement of CRM and resuming treatment will restart the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a maintenance dose administered Q2W, or Q4W for the lowest weight group on the reduced CZP regimen for the duration of the study (see Table 7-1).

7.2.1 Procedure for dose change (Protocol Amendment 9)

Following Protocol Amendment 9, study participants will only be enrolled on the original CZP dose regimen. With Protocol Amendment 4, the maintenance dose in the study was reduced by 50% for all weight groups (not applicable for study participants enrolled on the reduced CZP dose regimen per Protocol Amendment 5). Participants on the reduced CZP dose regimen can remain on the reduced CZP dose or may be switched to the original CZP dose regimen at the discretion of the Investigator and in consultation with the medical monitor. Additional dose changes are not allowed. The procedure for dose change is as follows:

- The timepoint of the dose change is the next scheduled time of injection after the Informed Consent form related to the dose change was signed. In case the next scheduled injection was planned for home dosing, the study participant will be requested to return to the clinic for an Unscheduled Visit for signing the Informed Consent form related to the dose change, administration of CZP, and to dispense the new supplies. Unused IMP dispensed previously needs to be returned.
  In case the study participant is not able to visit the site for that next scheduled injection, then the dose change must be performed at the next scheduled injection.

- Study participants will be monitored at least every 4 weeks over a period of 12 weeks after the dose change, either at the regularly scheduled visits or at additional Unscheduled Visits. The Unscheduled Visits will be scheduled to match with the dosing schedule, ie, the study medication will be administered at the day of the Unscheduled Visit. The Investigator should consult with the Medical Monitor in case of any questions related to the timing of the dose change or the Unscheduled Visits.
  - Study participants undergoing the dose change at an Unscheduled Visit between the regular visits will be required to return at the latest after 4 weeks for an Unscheduled Visit in case no regular visit is scheduled within 4 weeks. These study participants will be monitored at least every 4 weeks over a period of 12 weeks.
- At Unscheduled Visits when the dose change occurs and following the dose change, the following will be assessed: AEs, concomitant medications and procedures, vital signs, hematology/biochemistry, as well as CRP, PRINTO/PRCSG standard joint examination, Physician's Global Assessment of Disease Activity, CHAQ, and Parent's Global Assessment of Overall Well-Being to determine PedACR response rates. Assessments at regular visits will be done as scheduled, except for PK sampling (see below).

7.3 Packaging

Certolizumab pegol is packaged and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. They are suitably packaged in such a way as to protect the IMPs from deterioration during transport and storage.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language. Details on Labeling will be provided in the Pharmacy manual.

7.5 Handling and storage requirements

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. All IMPs must be stored in a secured, limited access area between 2 and 8°C (35.6 and 46.4°F) and protected from light.

Appropriate storage conditions must be ensured either by controlled temperature or by completing a temperature log in accordance with local requirements, but at least once a day with minimum and maximum temperatures reached over the time interval. A temperature out-of-range can be noted during storage at a site or during shipment at any time during the study.

In case a temperature out-of-range is noted during storage at a site, it must be immediately communicated to the Clinical Program Manager (CPM) (or designee) via the monitor before further use of the IMP. Site personnel have to complete the temperature excursion form during storage and fax it together with the temperature log form to the monitor. The monitor immediately has to inform Clinical Trial Supplies (CTS) at UCB who will place the affected medication in quarantine during the evaluation of the temperature excursion.

In case a temperature out-of-range is noted during shipment to a site, it must be immediately put in quarantine by contacting the IXRS and informing the monitor during the evaluation of the temperature excursion. For the maximum of information the temperature monitoring device has to be sent back immediately to the distributor.

After the evaluation of the temperature excursion, CTS will provide the monitor and the IXRS with instructions regarding further use of the product at the site.

For IMP dispensed to the study participant/caregiver for injection at home, the Investigator (or designee) will instruct the study participant/caregiver to store the IMP following the instructions on the label.

7.6 Drug accountability

A drug accountability form will be used to record IMP dispensing and return information on a by-study participant basis and will serve as source documentation during the course of the study. Details of any IMP lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

Periodically and at the end of the study, all unused and expired investigational product (PFSs and containers) will be collected and sent to the Sponsor (or designee) for destruction. All used PFSs will be disposed of by site staff in an acceptable disposal (sharps) container directly after the administration. For CZP administration at home, the study participant/caregiver will receive a disposal (sharps) container in order to return used PFSs to the site for disposal. All containers of the used PFSs must be kept until the accountability is checked by the monitor and can be destroyed afterwards.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the IMP is used only in accordance with the protocol.

7.7 Procedures for monitoring study participant compliance

At each visit after IMP is dispensed, study participants must return all used, unused, and partially used IMP containers together with the documentation on home dosing, if applicable. Drug accountability must be done in the study participant's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

If a study participant is found to be persistently noncompliant (missing 2 or more consecutive scheduled CZP doses or missing 3 or more doses over a 12-month period), the Sponsor in conjunction with the Investigator will make a decision as to whether the study participant should be withdrawn from the study.

This rule does not apply when CZP is discontinued if the study participant is in CRM or if CZP is temporarily discontinued due to an AE. The study participant will continue with

scheduled study visits even if not dosed. In the case of temporary discontinuation due to an AE, the Sponsor in conjunction with the Investigator will make a decision as to whether the study participant should be withdrawn from the study.

7.8 Concomitant medication(s)/treatment(s)

The sections below describe the following categories of concomitant medications/treatments: concomitant medications that are permitted during the study, rescue medications that are allowed before Week 16, rescue medications that are allowed after Week 16 and may be used for the remainder of the study, and concomitant medications that are prohibited at any time during the study.

7.8.1 Permitted concomitant treatments (medications and therapies)

The following are permitted:

- MTX, if being used:
  - Must have been stable for at least 1 month before Screening (Visit 1) at ≥10 to ≤15mg/m^2 per week.
  - During the study, an increase is allowed only after Week 16 and to a maximum dose of 15mg/m^2 per week.
  - Prior to Week 16, route of administration must not change. After Week 16, the route of administration may be changed.
  - During the study, the MTX dose may be decreased, but not discontinued. Methotrexate may be discontinued only for documented reasons of intolerance or toxicity, or in study participants who achieve CRM (persistent CID over a period of 6 months, as defined in Section 11.10) and only after discontinuation of CZP.
  - Study participants who do not maintain persistent CID following achievement of CRM can reinitiate therapy with MTX.
- Scheduled and as needed (PRN) use of NSAIDs, cyclooxygenase-2 (COX-2) inhibitors, acetaminophen (paracetamol), and other analgesics are permitted.
- Folic acid or folinic acid.
- Topical anesthetic creams (eg, lidocaine/prilocaine creams, licensed NSAID creams).
- Corticosteroids:
  - At study entry, the dose should have been stable for at least 7 days prior to the Baseline joint examination at a maximum dose of 10mg or 0.2mg/kg prednisone (or equivalent) per day, whichever is the smaller dose.
  - During the study, the dose of oral corticosteroids may be decreased but not initiated or increased above 10mg or 0.2mg/kg prednisone (or equivalent) per day, whichever is the smaller dose. The dose must be stable in the 7 days prior to a joint examination.
  - Initiation of topical corticosteroids is allowed for treatment of uveitis if developed during the course of the study.

- Intra-articular (ia) corticosteroids may be administered no more frequently than every 4 months and no more than up to 3 times in 1 year and only into up to 2 joints at a single time point.
- Any joint injected with ia corticosteroids will be excluded from the efficacy analysis for a period of 3 months.
- Intravenous (iv) corticosteroid use is permitted only for stress dosing for the purposes of surgery.

- Oral/parenteral/implantable hormonal contraceptives (stable for at least 2 months prior to Screening [Visit 1] if initiated prior to entering the study).
- Non-live and therefore permitted vaccinations include: intramuscular polio, Hepatitis A, Hepatitis B, pneumococcal conjugate vaccine (PCV), pneumococcal polysaccharide vaccine (PPSV), diphtheria-tetanus-pertussis (DTaP/DTP), Hemophilus influenzae type b (Hib), injectable (but not nasal) influenza, meningococcus, and human papilloma virus. The effectiveness of vaccines administered while on CZP treatment is currently unknown. (Live or live attenuated vaccines are prohibited during the course of the study.)

7.8.2 Rescue medication

Rescue medication use is defined as any initiation of treatment or increase in dose of a medication used to treat JIA (in addition to the IMP) that is considered to impact the efficacy analyses. A study participant requiring rescue medication after first administration of IMP is considered as a treatment failure from that time point forward for the purpose of efficacy analyses. Exception: A study participant initiating rescue medication use after the Week 56 visit will not be considered a treatment failure and the efficacy data will be analyzed as observed without imputation.

A study participant requiring rescue medication may remain on study medication if the benefit/risk assessment of the study participant's continued participation is still favorable based on the Investigator's clinical assessment.

The use of rescue medication should be specifically avoided during the first 4 months (16 weeks) of treatment, if possible.

The following medications are defined as rescue medication in the first 16 weeks of this study:

- Initiation of MTX (if not being used at study entry), or increase of MTX above Baseline.
- Initiation of oral corticosteroids, or increase above Baseline.

The following medications are defined as rescue medication after Week 16:

- Initiation of MTX (if not being used at study entry), and increase of MTX above 15mg/m^2 per week at any time.
- Initiation of oral corticosteroids, or increase to >10mg or 0.2mg/kg prednisone (or equivalent) per day, whichever is the smaller dose.

The following medications are defined as rescue medication when given at any time during the study:

- Injection of intra-articular (ia) corticosteroids into more than 2 joints at a single time point.
- Injection of intra-articular (ia) corticosteroids into the same joint more frequently than 3 times in a 12-month period.
- Intravenous (iv) corticosteroids (any dose), if not used for stress dosing for the purposes of surgery.
- Intramuscular (im) corticosteroids.

Use of the following medications only results in efficacy data at the next scheduled visit being treated as missing/nonresponse:

- Higher than Baseline dose of NSAIDs and COX-2 inhibitors including PRN use within 72 hours prior to scheduled study visit.
- Higher than Baseline dose of analgesics or opioids including PRN use within 48 hours prior to scheduled study visit.
- Any increase in dose of oral corticosteroids within 7 days prior to scheduled study visit.

All concomitant medications and procedures must be recorded on the CRF. Rescue medication will not be supplied by the Sponsor.

7.8.3 Prohibited concomitant treatments (medications and therapies)

See Table 6-1 for prohibitions prior to study entry. The following are prohibited at any time during the study:

- Nonbiologic DMARDs (other than MTX; see Section 7.8.1) and biologic DMARDs.
- Any experimental (biological or non-biological) therapy (within or outside a clinical study).
- Live and live attenuated vaccinations including, but not limited to, oral polio, chicken pox (varicella), measles-mumps-rubella (MMR), nasal influenza, and rotavirus. No data are available on the response to live vaccinations or the secondary transmission of infection by live vaccines in study participants receiving CZP.

The concomitant use of these must result in the study participant's immediate discontinuation of CZP dosing and the study participant must be withdrawn from the study.

7.9 Lost to follow up

For study participants considered as lost to follow up, the Investigator should make an effort (at least 1 phone call and 1 written message to the participant), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (at least 1 phone call and 1 written message to the participant), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up documented in the eCRF.

7.10 Enrollment and numbering of study participants

To enroll a study participant, the Investigator must contact the IXRS and provide brief details of the study participant to be enrolled, eg, age, weight, and concomitant MTX use. The Investigator will enter the unique study participant number assigned to each study participant, based on a predefined range of study participant numbers assigned to the Investigator's site. This unique study participant number will be required in all communications between the Investigator (or designee) and the IXRS regarding a particular study participant. The IXRS will allocate container numbers to the study participants based on the unique study participant number during the course of the study. Study participant numbers and container numbers will be tracked via the IXRS and also will be required to be entered into the CRF.

The IXRS will allocate containers of study medication as appropriate to the visit schedule.

8 STUDY PROCEDURES BY VISIT

During the study, the visits will take place in the timeframe as described in the study schedule (Schedule of study assessments, Section 5.2). The acceptable window between all the study visits is +/-3 days **relative to Baseline** (Week 0, Visit 2).

8.1 Visit 1 (Week -4 to 0) Screening

Prior to any study activities and at least 4 days prior to the Baseline Visit (Visit 2), study participants and parent(s)/legal representative, as applicable, will be asked to read and sign an Informed Consent/Assent Form that has been approved by an IRB/IEC and which complies with regulatory requirements. Study participants and parent(s)/legal representative will be given adequate time to consider any information concerning the study given to them by the Investigator or designee. As part of the informed consent procedure, study participants and

parent(s)/legal representative will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study.

Assessments at this visit will include:

- Obtain written informed consent/assent
- Assessment of inclusion/exclusion criteria
- Demographic data including date of birth, gender, and race/ethnicity
- JIA history and prior JIA medication
- Review of general medical and procedure history, concomitant diseases, and previous and concomitant medications
- Vital signs
- Height*
- Weight*
- Physical examination
- TB questionnaire
- Hematology/biochemistry/urinalysis (including hepatitis and HIV testing)
- Reproductive potential and birth control
- Pregnancy (serum) test for postmenarcheal females
- CRP
- Chest radiographic imaging and results must be available at Baseline before first IMP administration unless a chest X-ray or CT scan is available from 2 months prior to Screening.
- TB screening: TST and IGRA for study participants from 2 to 4 years of age (unless the study participant is located in a country with high TST positivity and/or written documentation for BCG vaccination is available) or IGRA (to be performed by the central lab) for study participants from 5 to 17 years of age. Note that the TST may be positive due to BCG vaccination, however, UCB will not permit enrollment of pediatric study participants <5 years old into the study without written approval from a physician with expertise in pediatric TB**
- TB questionnaire (study participant and parent/caregiver)**
- PRINTO/PRCSG standard joint examination
- Physician's Global Assessment of Disease Activity (VAS)
- CHAQ-parent reported
- Parent's Assessment of Arthritis Pain (VAS)
- Parent's Global Assessment of Overall Well-Being (VAS)

- Adverse events
- IXRS contact (to register study participant with unique study participant number)

*Change in height and weight over the last 6 months and over the last year will be collected via parent-/self-report, if not available from medical records.

**For details of TB screening and testing, see Section 10.7.9.

8.2 Visit 2 (Week 0) Baseline

- Assessment of inclusion/exclusion criteria
- Vital signs (within approximately 15 minutes prior to dosing and [pulse and blood pressure only] approximately 30 minutes after dosing)
- Height
- Weight (measurement used to determine CZP dose according to Table 7-1)
- Tanner stages (except growth)
- Physical examination
- TB questionnaire (study participant and parent/caregiver)
- Hematology/biochemistry/urinalysis (only if in the Investigator's opinion there is a change in the study participant's status compared to the Screening Visit, ie, any valid result from hematology, biochemistry, or urinalysis obtained at the Screening Visit will be used as the Baseline value)
- Reproductive potential and birth control
- Pregnancy (urine) test for postmenarcheal females
- CRP
- PRINTO/PRCSG standard joint examination
- Physician's Global Assessment of Disease Activity (VAS)
- CHAQ-parent reported
- Parent's Assessment of Arthritis Pain (VAS)
- Parent's Global Assessment of Overall Well-Being (VAS)
- DMS
- JADAS
- FPS-R for study participants ages 5 to 11 years (at Baseline and daily assessment on Day 1 to Day 7)
- JIA Pain VAS for study participants ages 12 to 17 years; acute and standard versions (both at Baseline and daily assessment of the acute version on Day 1 to Day 7)
- Fatigue Assessment Scale

- Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey
- Concomitant medications and procedures
- Adverse events
- IXRS contact (to receive assigned container number[s])
- CZP plasma concentrations
- Anti-CZP antibodies
- Autoantibodies (ANA antibodies and, if ANA is positive, anti-dsDNA antibodies)
- CZP administration (Injection by site personnel including demonstration for training.)

Documentation of the assessment of all 6 core set measures of PedACR response (PRINTO/PRCSG standard joint examination, Physician's Global Assessment of Disease Activity [VAS], CHAQ-parent reported, Parent's Assessment of Arthritis Pain [VAS], Parent's Global Assessment of Overall Well-Being [VAS] and CRP) **will be submitted to UCB or designee for immediate review of completeness, while the study participant is still on site.**

8.3 Visits 3 and 4 (Weeks 1 and 2)

- Vital signs (within approximately 15 minutes prior to dosing and [pulse and blood pressure only] approximately 30 minutes after dosing)
- Weight (at Week 2 measurement used to reassess CZP dose according to Table 7-1)
- CRP
- PRINTO/PRCSG standard joint examination
- Physician's Global Assessment of Disease Activity (VAS)
- CHAQ-parent reported
- Parent's Assessment of Arthritis Pain (VAS)
- Parent's Global Assessment of Overall Well-Being (VAS)
- Collection of JIA Pain VAS or FPS-R completed on Day 1 to Day 7
- Clinically Inactive Disease
- DMS
- JADAS
- Fatigue Assessment Scale
- Concomitant medications and procedures
- Adverse events
- IXRS contact
- CZP plasma concentrations (Week 1 only)

- Anti-CZP antibodies (Week 1 only)
- CZP administration (Week 2 only. Self/or parent/caregiver-administration under the supervision of the site staff for training.)

8.4 Visits 5 to 10 (Weeks 4, 8, 12, 16, 20, and 24)

- Vital signs (within approximately 15 minutes prior to dosing and [pulse and blood pressure only] approximately 30 minutes after dosing)
- Height (Week 24 only)
- Weight (measurement used to reassess CZP dose according to Table 7-1)
- Tanner stages (except growth; Week 24 only)
- Physical examination
- TB questionnaire (study participant and parent/caregiver) (Weeks 12 and 24 only)
- Hematology/biochemistry/urinalysis
- Reproductive potential and birth control
- Pregnancy (urine) test for postmenarcheal females (Weeks 8, 16, and 24 only)
- CRP
- PRINTO/PRCSG standard joint examination
- Physician's Global Assessment of Disease Activity (VAS)
- CHAQ-parent reported
- Parent's Assessment of Arthritis Pain (VAS)
- Parent's Global Assessment of Overall Well-Being (VAS)
- Clinically Inactive Disease
- Clinical remission on medication (at Week 24 only)
- DMS
- JADAS
- FPS-R for study participants ages 5 to 11 years (Weeks 4, 12, 16, and 24 only)
- JIA Pain VAS (standard version, Weeks 4, 12, 16, and 24 only for study participants ages 12 to 17 years)
- Fatigue Assessment Scale (Weeks 4, 8, 16, and 24 only)
- Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey
- Concomitant medications and procedures
- Adverse events
- IXRS contact (Assignment of all required study medication until next scheduled visit.)

- CZP plasma concentrations (predose at Weeks 4, 12, 16, and 24.
  Study participants will return to the clinic site for a **postdose CZP plasma sample** approximately **5 to 7 days following the Week 16 visit**.)
- Anti-CZP antibodies (predose at Weeks 4, 12, 16, and 24)
- Autoantibodies (ANA and anti-dsDNA antibodies) (Week 16 only)
- CZP administration (At Week 4, self/parent/caregiver-administration under the supervision of the site staff for training. After Week 4, administration of study medication either by site personnel [for those not performing home-based administration] or self/parent/caregiver-administration under supervision of site personnel to ensure proper injection technique.)

Between scheduled visits (Weeks 6, 10, 14, 18, 22, 26, 28, 30), CZP will be administered at home by the study participant or parent/caregiver or study participants may visit the site for CZP administration by staff personnel.

Documentation of the **Week 24** assessment of all 6 core set measures of PedACR response (PRINTO/PRCSG standard joint examination, Physician's Global Assessment of Disease Activity [VAS], CHAQ-parent reported, Parent's Assessment of Arthritis Pain [VAS], Parent's Global Assessment of Overall Well-Being [VAS] and CRP) **will be submitted to UCB or designee for immediate review of completeness, while the study participant is still on site.**

8.5 Visits 11 and continuing (Week 32 and every 8 weeks thereafter)

For study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8, provided that compliance is maintained with the CZP dosing schedule using at-home administration.

- Vital signs (within approximately 15 minutes prior to dosing and [pulse and blood pressure only] approximately 30 minutes after dosing)
- Height (Week 48 and every 24 weeks thereafter; for study participants enrolled prior to Protocol Amendment 9, height assessment will be performed every 48 weeks following Protocol Amendment 8)
- Weight (measurement used to reassess CZP dose according to Table 7-1)
- Tanner stages (except growth; for study participants enrolled prior to Protocol Amendment 9, Tanner stages assessment will be performed every 48 weeks following Protocol Amendment 8, and only for those subjects who have not reached Tanner stage V)
- Physical examination
- TB screening once a year (at least every 48 weeks)

- TB questionnaire (study participant and parent/caregiver) (Week 40 and every 16 weeks thereafter)
- Hematology/biochemistry/urinalysis
- Reproductive potential and birth control
- Pregnancy (urine) test for postmenarcheal females
- CRP
- PRINTO/PRCSG standard joint examination
- Physician's Global Assessment of Disease Activity (VAS)
- CHAQ-parent reported
- Parent's Assessment of Arthritis Pain (VAS)
- Parent's Global Assessment of Overall Well-Being (VAS)
- Clinically Inactive Disease
- Clinical remission on medication
- DMS
- JADAS
- FPS-R for study participants ages 5 to 11 years
- JIA Pain VAS (standard version, ages 12 to 17 years)
- Fatigue Assessment Scale
- Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey
- Concomitant medications and procedures
- Adverse events
- IXRS contact (Assignment of all required study medication until next scheduled visit.)
- CZP plasma concentrations (for study participants enrolled following Protocol Amendment 9 only; Weeks 32, 40, and 48 and every 24 weeks thereafter)
- Anti-CZP antibodies (for study participants enrolled following Protocol Amendment 9 only; Weeks 32, 40, and 48 and every 24 weeks thereafter)
- Autoantibodies (ANA and anti-dsDNA antibodies) (Week 48 only)
- CZP administration (Administration of study medication either by site personnel or self/parent/caregiver-administration under supervision of site personnel to ensure properly performed.)

Between scheduled visits (starting at Week 34), CZP will be administered at home by the study participant or parent/caregiver or study participants may visit the site for CZP administration by staff personnel.

8.6 Unscheduled Visit

- Vital signs (within approximately 15 minutes prior to dosing and [pulse and blood pressure only] approximately 30 minutes after dosing, if dosing is applicable)
- Concomitant medications and procedures
- Adverse events

Other PK and safety assessments should be performed as related to nature of the visit.

8.6.1 Unscheduled Visit related to dose change

If required, study participants will return for an Unscheduled Visit to undergo the dose change. Study participants will be monitored at least every 4 weeks over a period of 12 weeks after the dose change, either at the regularly scheduled visits or at additional Unscheduled Visits.

The following will be assessed at this visit:

- Administration of study medication
- Adverse events
- Concomitant medications and procedures
- Vital signs (within approximately 15 minutes prior to dosing and [pulse and blood pressure only] approximately 30 minutes after dosing)
- Hematology/biochemistry
- CRP
- PRINTO/PRCSG standard joint examination
- Physician's Global Assessment of Disease Activity (VAS)
- CHAQ-parent reported
- Parent's Global Assessment of Overall Well-Being (VAS)
- IXRS contact, if applicable

8.7 Early Discontinuation/End of Treatment Visit

- Vital signs
- Height
- Weight
- Tanner stages (except growth)
- Physical examination
- TB questionnaire (study participant and parent/caregiver)
- Hematology/biochemistry/urinalysis

- Reproductive potential and birth control
- Pregnancy (urine) test for postmenarcheal females
- CRP
- PRINTO/PRCSG standard joint examination
- Physician's Global Assessment of Disease Activity (VAS)
- CHAQ-parent reported
- Parent's Assessment of Arthritis Pain (VAS)
- Parent's Global Assessment of Overall Well-Being (VAS)
- Clinically Inactive Disease
- Clinical remission on medication
- DMS
- JADAS
- FPS-R for study participants ages 5 to 11 years
- JIA Pain VAS (standard version ages 12 to 17 years)
- Fatigue Assessment Scale
- Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey
- Concomitant medications and procedures
- Adverse events
- IXRS contact (to register study participant visit)
- CZP plasma concentrations (for study participants enrolled following Protocol Amendment 9 only
- Anti-CZP antibodies (for study participants enrolled following Protocol Amendment 9 only)
- Autoantibodies (ANA and anti-dsDNA antibodies)

8.8 Final Visit

The final visit is to be completed by all study participants 12 weeks after the final dose of CZP.

- Vital signs
- Weight
- Physical examination
- Hematology/biochemistry/urinalysis
- Reproductive potential and birth control

- Pregnancy (urine) test for postmenarcheal females
- Concomitant medications and procedures
- Adverse events
- IXRS contact (to deactivate the study participant)
- CZP plasma concentrations (for study participants enrolled following Protocol Amendment 9 only)
- Anti-CZP antibodies (for study participants enrolled following Protocol Amendment 9 only)

9 ASSESSMENT OF PHARMACOKINETICS AND IMMUNOLOGICAL VARIABLES

Blood samples will be collected predose to determine plasma concentrations of CZP and anti-CZP antibodies at Baseline (Week 0), Weeks 4, 12, 16, 24, 32, 40, 48, and then every 24 weeks thereafter; the Early Discontinuation/End of Treatment Visit, and the Final Visit 12 weeks after the last dose of study medication. For study participants enrolled prior to Protocol Amendment 9, samples for CZP plasma concentration and anti-CZP antibodies will no longer be collected. In addition, blood samples will be collected 5 to 7 days after dosing at Baseline (ie, at Week 1, Visit 3) and Week 16 (ie, return of study participant to clinic site at Week 17) to determine postdose plasma concentration.

All of these blood draws (except for postdose samplings at Week 1 and after Week 16) will be performed prior to any study medication administration, where applicable, and all of them coincide with the blood collection times for the assessment of hematology and clinical chemistry parameters, so that no additional blood draws are required at these visits except at Week 1 (Visit 3) and the postdose sampling following Week 16 (Visit 8). Time and date of each blood draw will be documented on the CRF.

Instructions on blood sample collection, processing, storage, and labeling/shipping will be provided in the laboratory manual for this study.

Blood samples to determine plasma concentrations of CZP and anti-CZP antibodies will be analyzed by a specialty laboratory. All study participants enrolled following Protocol Amendment 9 will have plasma concentrations of CZP and anti-CZP antibodies analyzed using an ECLIA method that meets current regulatory standards. In addition, PK and ADA samples (for which sufficient volume is available) collected in this study prior to Protocol Amendment 9 will be analyzed with the ECLIA method. The collective ECLIA-based PK data for this study will form the basis of any future CZP modeling and simulation work.

These plasma samples may be used additionally for analyses of CZP and its constituent moieties using alternative assay methods. The results of the analyses of CZP and its constituent moieties from alternative methods may be reported separately.

10 ASSESSMENT OF SAFETY

10.1 Adverse events

10.1.1 Definition of AE

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

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after signing the Informed Consent Form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the CRF even if no IMP was administered but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all medical conditions or AEs which recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the study participant's history or the period preceding Baseline.

10.1.2 Procedures for reporting and recording AEs

The study participant/caregiver 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 (your child's) health (since your last visit)?"

In addition, the Investigator should review any self-assessment procedures (eg, diary cards) employed in the study to identify potential AEs.

10.1.3 Description of AEs

When recording an AE, the Investigator should report an overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs, where possible. If a diagnosis/syndrome is eventually determined, relevant signs and symptom AEs should be consolidated under the diagnosis/syndrome rather than continued to be listed individually. The CRF and source documents should be consistent. Any discrepancies between the study participant's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event CRF (including judgment of relationship to study medication) are described in the CRF instructions.

10.1.4 Follow-up on AEs

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

If an AE is still ongoing at the end of the study for a study participant, follow-up should be provided until the AE resolves/reaches a stable level of sequelae, the Investigator no longer deems that it is clinically significant, or the study participant is lost to follow-up. If no follow-up is provided, the Investigator must provide a justification. Follow-up of any ongoing AE is continued until the end of the study for a study participant (Final Visit) or until the study participant is lost to follow-up.

10.1.5 Rule for repetition of an AE

An increase in the intensity of an AE (or an ongoing medical condition at the study onset) 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,
- Change in intensity or severity being recorded.

10.1.6 Reporting requirements for events relating to TB

Reporting requirements for events relating to TB Tuberculosis is a safety topic of interest. The safety topics of interest are selected based on findings from the IMP clinical program to date, potential risks generally associated with biologic immunomodulators, or findings from other medicines with a related mechanism of action. There are no specific AE reporting requirements beyond those specified for AEs and SAEs in the protocol; however, special monitoring, additional data collection activities, and/or enhanced signal detection activities (within UCB) are in place. The reporting requirements for events relating to TB are as follows:

- IGRA test conversions defined as a positive or indeterminate (and confirmed indeterminate on repeat) should be reported as AEs. The AE term would need to be updated with final diagnosis once available.
- LTBI must be reported as an AE. Follow-up reports should be completed as per protocol requirement until the LTBI resolves.
- Confirmed active TB is always considered a SAE and must be reported per SAE reporting instruction in the study protocol. Follow-up reports should be completed as per protocol requirement until TB infection resolves.

10.1.7 Pregnancy

Should a study participant become pregnant after the first intake of IMP, UCB Patient Safety should be informed immediately. Study medication must be discontinued as soon as pregnancy is known (by positive pregnancy test). Study participants can remain in the study under observation and should attend to scheduled visits regularly as their condition allows.

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

In cases where the partner of a male study participant enrolled in a clinical trial becomes pregnant, UCB will ask the Investigator or designee to contact the study participant 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 study participant's partner (or parent/caregiver if study participant underaged) for completion.

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

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

A pregnancy becomes a serious adverse event (SAE) in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. A pregnancy is considered as an SAE in case of contraceptive failure (eg, pill taken everyday at approximately the same time each day without having been forgotten or with use of permanent contraceptive devices). Those serious events must be additionally reported using the Investigator SAE report form.

10.1.8 Suspected transmission of an infectious agent via a medicinal product

For the purposes of reporting, any suspected transmission of an infectious agent via the study medication should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the CRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

10.1.9 Overdose of IMP

Excessive dosing of IMP (beyond that prescribed in the protocol and including overdose) should be recorded in the appropriate CRF module. Since excessive dosing may be symptomatic, in that the excessive dosing results in clinical signs and symptoms, or the excessive intake may itself be a symptom, any SAE or nonserious AE associated with excessive dosing must be followed as any other serious or nonserious AE.

10.1.10 Ongoing safety data review and oversight

This study will be performed using remote data capture (RDC). The Investigator is responsible for the prompt reporting of accurate, complete, and legible data in the electronic CRFs. Laboratory data will be regularly transferred electronically to the Sponsor for incorporation with the Investigator-entered data.

Adverse event and laboratory data will periodically be reviewed by medically qualified personnel at UCB knowledgeable about the disease and treatment. Regular monitoring of all safety data collected during CZP clinical studies is performed as described in the Safety Signal Detection in the Ongoing Clinical Trials Charter for CZP. The data from this study will be reviewed separately, in the context of all CZP data, and in the context of data coming

from any other pediatric studies. In addition, a Data and Safety Monitoring Board (DSMB) will periodically review emerging safety and efficacy data (see Section 13.7). The DSMB will function and meet on a regular basis as per the agreed upon charter.

The Sponsor Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Patient Safety and Data Management representatives.

10.2 Serious adverse events

10.2.1 Definition of SAE

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

- Death.
- Life-threatening.
    - Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.
- Significant or persistent disability/incapacity.
- Congenital anomaly/birth defect (including that occurring in a fetus).
- Important medical event that, based upon appropriate medical judgment, may jeopardize the study participant and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of an SAE: allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, pregnancy due to contraceptive failure, or the development of drug dependency or drug abuse.
- Initial inpatient hospitalization or prolongation of hospitalization.
- A study participant admitted to a hospital, even if released on the same day, meets the criterion initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criterion. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of an SAE (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. Preplanned surgery or elective surgery must be verified in source document prior to Baseline (eg, timing and type of procedure). For example, if a study participant 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 definition. Please note that, if the pre-existing condition has worsened or manifested in an

unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.

Hospitalization for diagnostic or therapeutic procedures in the absence of any associated AE will not be considered as an SAE, except when otherwise required by regulatory authorities. Preplanned diagnostic or therapeutic procedures must be verified in source document prior to Baseline (eg, timing and type of procedure). If a hospitalization is planned prior to the study participant receiving the first dose of IMP (at Week 0), it will not be classified as either an AE or SAE. This also applies to a scheduled elective surgery where no AE is present. A noncomplicated, preplanned elective surgery will not be considered an AE or SAE even if it involves hospitalization. However, if a hospitalization is unplanned or is a result of an AE, this will be considered to be an SAE.

10.2.2 Procedures for reporting SAEs

If an SAE is reported, UCB 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 Investigator must forward to UCB (or its representative) a duly completed Investigator SAE Report form provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the pharmacovigilance database.

An Investigator SAE Report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE report form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each study participant, and to also inform participating study participants of the need to inform the Investigator of any AE within this period. Any SAEs that the Investigator suspects may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the CZP IB.

10.2.3 Follow-up of SAEs

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

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

10.3 AEs of special interest

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

Adverse events of special interest include:

- Potential Hy's Law
  - Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.
- Serious infections, including opportunistic infections
- Malignancies, including lymphoma
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leukopenia
- Serious bleeding events
- Lupus and lupus-like syndrome
- Serious skin reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrosis, and erythema multiforme)

Adverse events of special interest must be reported immediately by the Investigator (see Section 10.4).

The purpose of the AESI is to identify and capture product specific AEs/reactions requiring expedited reporting or close monitoring by 1 or more regulatory authorities or close monitoring required by UCB. This tool will help ensure that specific special reporting requirements from regulatory authorities and safety topics requiring close monitoring are appropriately identified, processed, reported, and monitored. The process also allows for detection of safety signals, signal evaluation, and the assessment of changes in the benefit-risk ratio of UCB products/compounds, based on all safety and benefit-risk information available for the protection of the patient.

10.4 Immediate reporting of AEs

The following AEs must be reported immediately via use of the SAE form (see Study Contact Information for contact details):

- SAE: AE that the Investigator classifies as serious by the aforementioned definitions (see Section 10.2.1) regardless of causality

- Suspected transmission of an infectious agent via a medicinal product
- AE of interest (see Section 10.3)

10.5 Anticipated serious adverse events

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

This list does not change the Investigator's obligation to report all serious AEs (including Anticipated SAEs) as detailed in Section 10.2.2.

Table 10-1 Anticipated serious adverse events for JIA population

Preferred Term
Juvenile idiopathic arthritis

10.6 Laboratory measurements

Hematology, biochemistry, and urinalysis samples will be collected at Screening, Baseline, Weeks 4, 8, 12, 16, 20, 24, 32 and every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8), the Early Discontinuation/End of Treatment Visit, and the Final Visit 12 weeks after the last dose of study medication. At Week 1, only CRP and PK samples will be collected and at Week 2, only CRP samples will be collected. In addition, hematology, biochemistry, and CRP samples will be collected at Unscheduled Visits for study participants undergoing a dose change (Section 7.2.1 and Section 8.6.1).

Retesting of laboratory assessments within the Screening Period is allowed in case of isolated exclusionary laboratory assessments at Screening if, in the Investigator's opinion, the value is not reflective of the study participant's previous clinical and laboratory pattern (see Section 6.3). In addition, retesting within the Screening Period is allowed in case of reporting failure of laboratory results (eg, issues with transportation of samples).

Study participants do not have to fast.

Laboratory criteria and collection details are provided in the laboratory manual.

For blood sampling on PK and immunological variables see Section 9.

Measures to minimize distress and pain have been considered for this study in line with the "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population" (European Medicines Agency, 2008) and the "Guidance for Industry – E11 Clinical Investigation of Medicinal Products in the Pediatric Population" (FDA, 2000). Unless in the Investigator's opinion there is a change in the study participant's status, any valid laboratory result obtained at the Screening Visit on hematology, chemistry, and urinalysis can be used as the Baseline value, which will avoid the repeated collection of these specific samples at Baseline. Only samples for CRP, PK, and immunological variables will then be collected at Baseline (Week 0).

A qualified central laboratory capable of handling small sample/tube sizes will be used in this study. The planned total blood volumes collected at a single time point (visit) will vary between 2mL and 9mL. The highest blood sampling frequency will occur during the first 4 weeks of the study. The maximum total volume collected during this period will be approximately 24mL (at the first 4 study visits).

In addition, treatment of the venipuncture site with an anesthetic cream prior to blood sampling is permitted.

The TB assessment by IGRA testing is required to be performed by the central lab; additional blood sampling of approximately 3mL will be required at Screening.

If the result of the IGRA test is indeterminate, the test may be repeated once. If positive or indeterminate on retest, the study participant must not be enrolled (Section 10.7.9.5).

For study participants from 2 to 4 years of age, TST and IGRA testing will be performed (except for study participants with documented BCG vaccination) as described in Section 10.7.9.8.2. In countries with high BCG vaccination or high TST positivity, only IGRA should be performed (Section 10.7.9.8.2). The TST may be positive due to BCG vaccination, however, UCB will not permit enrollment of pediatric study participants <5 years old into the study without written approval from a physician with expertise in pediatric TB. IGRA testing should be done once a year (approximately every 48 weeks) for all study participants.

The central laboratory will analyze and assess blood and urine samples for the following (except dip stick test and urine pregnancy test); other PK assessments may be periodically performed as per Section 9:

Table 10-2 Laboratory measurements

Hematology	Serum biochemistry	Urinalysis
Red blood cells Hemoglobin Hematocrit Platelets White blood cells Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Sodium Potassium Chloride Bicarbonate Total calcium Inorganic phosphorus Creatinine kinase Glucose Creatinine Uric acid Urea Total protein Albumin Alkaline phosphatase Gamma glutamyl transferase Aspartate aminotransferase Alanine aminotransferase Lactate dehydrogenase Bilirubin Total cholesterol CRP Autoantibodies (ANA and anti-dsDNA antibodies)	pH[a] Protein[a] Glucose[a] Blood[a] Microscopy (WBC, RBC, casts, crystals, bacteria) (Microscopy will be performed only when there are abnormalities on dipstick)[a]
		Serum and urine pregnancy test[b]
		Hepatitis screening[c]
		HBcAb HBsAb HBsAg HCVAb HBV DNA, if applicable HCV RNA, if applicable
		TB screening[d]
		IGRA, TST
		HIV Screening
		HIV antigen or antibody

ANA=antinuclear antibody; anti-dsDNA antibodies=double-stranded deoxyribonucleic acid antibody; BCG=Bacille Calmette-Guérin; CRP=C-reactive protein; DNA=deoxyribonucleic acid; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; RBC=red blood cells; TB=tuberculosis; TST=tuberculin skin test; WBC=white blood cells
Note: The Screening Visit must be completed at least 4 to 12 working days prior to the Baseline Visit, depending on regional requirements and laboratory assessments required for the study participant (refer to laboratory manual for country-specific requirements). In case HBV DNA or TB IGRA is to be analyzed, the Baseline Visit can be performed at the earliest 12 days after the Screening Visit (6 working days in Russia). Study participants can only be enrolled into the study after all laboratory results of the Screening Visit have been confirmed.

[a] Urine dipsticks will be done locally at the site; only abnormalities will be reported. In case of abnormalities on dipstick, microscopy will be performed by the central laboratory.

[b] Serum pregnancy tests will be performed at Screening by the central laboratory (see Section 10.7.7). At Baseline, Weeks 8, 16, 24, and every visit thereafter, urine pregnancy tests will be performed locally.

[c] At Screening, laboratory testing includes testing for hepatitis B core antibody, hepatitis B surface antibody, hepatitis B surface antigen, hepatitis C virus antibody, and HIV 1/2. Study participants with a positive HBV test will not be allowed in the study (except for anti-hepatitis B positive only, in case study participant is immune due to well-documented hepatitis B vaccination or isolated false-positive anti-HBc test confirmed with a confirmatory test such as hepatitis B virus deoxyribonucleic acid [HBV-DNA]). A positive hepatitis C antibody test will be confirmed by a confirmatory test (such as HCV RNA) and those with a positive confirmatory test will not be allowed in the study.

[d] For TB testing refer to Section 10.7.9. IGRA is performed by the central lab.

10.7 Other safety measurements

10.7.1 Vital signs

Vital signs will be measured within approximately 15 minutes prior to dosing and in addition (pulse and blood pressure only) approximately 30 minutes after dosing with study medication. Study participants should be sitting for at least 5 minutes prior and during the collection of blood pressure and pulse rate measurements. Vital signs are as follows:

- Pulse
- Systolic/diastolic blood pressure measurement
- Temperature

Vital signs will be measured at Screening, Baseline, every visit (including all Unscheduled Visits) through the Early Discontinuation/End of Treatment Visit, and the Final Visit 12 weeks after the last dose of study medication.

10.7.2 Growth (height and weight)

Height will be recorded at Screening, Baseline, every 24 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, the height assessment will be performed every 48 weeks following Protocol Amendment 8), and the Early Discontinuation/End of Treatment Visit. Height will be recorded after the shoes have been removed. Height should preferably be measured with a wall-mounted stadiometer.

At Screening, change in height and weight over the last 6 months and over the last year will be collected via parent-/self-report, if not available from medical records.

Weight will be recorded after removal of shoes and heavy clothing. Weight will be measured at Screening, Baseline, and every visit through the Early Discontinuation/End of Treatment Visit, and the Final Visit 12 weeks after the last dose of study medication.

Results of the weight measurement will be used to determine the study participant's CZP dose as specified in Table 7-1.

10.7.3 Tanner stages

Assessments of study participants' developmental stages on external genitalia and pubic hair (boys) and on breast and pubic hair (girls) will be performed to determine Tanner stages (Marshall and Tanner, 1969; Marshall and Tanner, 1970). These assessments will be performed at Baseline and every 24 weeks thereafter, and the Early Discontinuation/End of Treatment Visit. For study participants enrolled prior to Protocol Amendment 9, Tanner stages assessment will be performed every 48 weeks following Protocol Amendment 8, and only for those subjects who have not reached Tanner stage V.

10.7.4 Physical examination

Physical examinations (except joint examination) will be performed at Screening, Baseline, Week 4, every visit thereafter through the Early Discontinuation/End of Treatment Visit, and the Final Visit 12 weeks after the last dose of study medication. Physical examination findings will be recorded in the CRF only at Screening. Details of the subsequent physical examinations should be recorded in the source documentation. Clinically relevant changes in subsequent physical examinations will be recorded as AEs.

The following body systems will be examined:

- General appearance
- Ear, nose, and throat
- Eyes
- Hair and skin
- Respiratory
- Cardiovascular
- Gastrointestinal
- Musculoskeletal
- Hepatic
- Neurological
- Mental status

10.7.5 Demographics, JIA history, prior JIA medication, and general medical and procedure history

Demographic data, JIA history including prior medication, general medical and procedure history (including any prior chest radiographs), and concomitant diseases will be recorded by the Investigator at the Screening Visit.

10.7.6 Reproductive potential and birth control

Reproductive potential of all study participants will be assessed by clinical questioning at Screening, Baseline, and every visit thereafter except at Visits 3 and 4 and at Unscheduled Visits. If the study participant is not of reproductive potential, the reason will be recorded (eg, prepubescent, pre-menarcheal). If the study participant is of reproductive potential and is sexually active, the method of birth control used will be recorded. Sexually active study participants (male and female) must use effective contraceptive measures (see Section 6.2, Exclusion Criterion 17).

10.7.7 Pregnancy testing

Pregnancy testing for all postmenarcheal female study participants (regardless of sexual activity) will consist of serum testing at Screening and urine testing at all other applicable visits. For female study participants who start menstruating during the study, urine pregnancy testing will be performed starting at the next applicable visit. Pregnancy testing must be carried out at Screening, Baseline, and every visit thereafter except at Unscheduled Visits (unless deemed necessary by the Investigator).

10.7.8 Autoantibody (ANA and anti-dsDNA antibodies) concentrations

Autoantibodies (ANA and anti-dsDNA antibodies) will be assessed at Baseline (testing for anti-dsDNA antibodies only if ANA is positive), Weeks 16 and 48, and the Early Discontinuation/End of Treatment Visit.

All of these blood draws will coincide with the blood collection times for the assessment of hematology and clinical chemistry parameters, so that no additional blood draws are required.

10.7.9 Assessment and management of TB and TB risk factors

As TNF inhibitors are known to be associated with significant risk of reactivation of LTBI or previously treated active TB, appropriate rigorous precautions are being taken within the protocol (see Section 6.2 [Exclusion Criterion 11] and Section 6.4 [Withdrawal Criterion 2]).

Study participants with known active TB disease, at high risk of acquiring TB infection, or with past or current LTBI or current or history of NTMB infection are excluded from the study.

a. Known TB infection whether present or past is defined as:

- Active TB infection or clinical signs and symptoms strongly suggestive of TB (pulmonary or extra pulmonary).
- History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection.

- Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the participant 's medical history.

b. High risk of acquiring TB infection is defined as:

- Known close exposure (eg, sleeping in the same room) to another person with active TB infection within 3 months prior to Screening.
- Time spent within 3 months prior to Screening in a healthcare delivery setting or institution where individuals infected with TB are housed or where the risk of transmission of infection is high.

c. LTBI is defined as an infection by mycobacteria tuberculosis with:

- A positive IGRA (or 2 indeterminate IGRAs), AND
- Chest imaging (or other imaging) negative for TB infection, AND
- Absence of signs, symptoms (eg, evidence of organ-specific involvement), or physical findings suggestive of TB infection.

d. Pulmonary NTMB infection is defined as a group of lung infections caused by mycobacteria different from mycobacterium tuberculosis infections.

10.7.9.1 Physical examination

The investigator should consider all potential sites of infection when assessing for TB during the physical examination and other evaluations and based on the study participant's medical or social history.

The most common primary focus of TB is the lung. Other sites may include gastrointestinal system, bones/joints, lymph glands and meninges etc. However, in immune compromised patients and/or patients treated with TNF inhibitors, extra-pulmonary manifestations of TB are common compared to normal population.

Some common symptoms that the study participant may present are dependent on the primary focus of infection and may include cough, blood in sputum, night sweats, lymphadenitis, joint pain/swelling, spinal deformity, headache/confusion, abdominal pain (mimicking IBD) etc. Unusual presentations should always be considered.

10.7.9.2 IGRA test conversion

Tuberculosis test conversion is defined as a positive or indeterminate (and confirmed indeterminate on repeat) IGRA result for the current test when previous IGRA test results were negative. All study participants with positive or indeterminate IGRA test results must immediately stop IMP administration. In case of an IGRA test conversion, the study participant must be considered as having either a suspected new latent or an active TB infection and be promptly referred to an appropriate specialist (eg, pulmonologist, infectious disease specialist) for further evaluation. Additional assessments (eg, blood tests or IGRA, chest X-rays, or other imaging) should be performed where medically relevant and documented. Such conversions should be reported as AEs as described in the protocol. The AE term would need to be updated with final diagnosis once available.

10.7.9.3 Latent TB infection

In case the evaluation by the appropriate specialist diagnoses a new LTBI, the study participant must permanently stop IMP and be withdrawn from the study. A TB prophylactic therapy in accordance with applicable clinical guidelines might be initiated, if considered appropriate.

Once withdrawn from study treatment, study participants should return for the Early Discontinuation Visit and complete all early discontinuation assessments, and complete an Final Visit (12 weeks after the last dose of IMP). LTBI must be reported as an AE. Follow-up reports should be completed as per protocol requirement until such time as the LTBI resolves.

10.7.9.4 Active TB or NTMB infection

Study participants who develop active TB or NTMB infection during the study must be withdrawn from the study. The study participant must be immediately discontinued from study medication and an Early Discontinuation Visit must be scheduled as soon as possible, but no later than the next scheduled visit. The study participant should be encouraged to keep the Final Visit as specified by the protocol. Treatment should be started immediately.

Note that study participants with history of or active NTMB infection are excluded from the study regardless of prior or current therapy for this condition.

Confirmed active TB is always considered an SAE. UCB's process requires that these must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting requirements. Follow-up reports should be completed as per protocol requirement until such time as the TB infection resolves.

10.7.9.5 TB assessment by IGRA or tuberculin skin test (TST)

During the Screening Period, the TB assessment by IGRA will be performed for all study participants (17 years and under). The IGRA (QuantiFERON®-TB GOLD In-Tube test) is the protocol-required method of screening for TB. A UCB validated central laboratory shall be responsible for interpreting the results of IGRA. The central laboratory must provide UCB with all assay values (both measured and calculated) in accordance with the approved test label or package insert. The IGRA negative result is as defined by the kit's manufacturer. If a central laboratory is not easily accessible for IGRA, UCB will determine whether the test should be performed by a qualified local laboratory.

If the result of the IGRA test is indeterminate, the test may be repeated once. If positive or indeterminate on retest, the study participant may not be enrolled. The retest must be done during the protocol-defined Screening window.

For study participants 6 to 17 years of age, the TST is optional in some regions/locations, based on local guidelines or requirements taking into account the prevalence of TB in such countries.

In countries with high *bacillus* Calmette-Guerin (BCG) vaccination or high TST positivity, it is not recommended to do the TST. The TST may be positive due to BCG vaccination. UCB will not permit enrollment of pediatric study participants without advice from physician with expertise in pediatric TB.

A positive TST is defined as an induration of ≥5mm occurring 48 to 72 hours after intradermal injection with 5 tuberculin units (TU) of either TST-S or 2TU of TST-RT23. The test must be performed and read by a TST qualified health care professional (per local guidelines). The exact measurement of the observed induration (in mm) must be documented in the study participant's medical record at the same time that it is read. Documentation must include the date and time the test was performed, the testing field (site), and the date and time the test was read.

During the conduct of the study, the TB assessment by IGRA can be repeated at the investigator's discretion. The TST test should not be repeated during the conduct of the study. The test results will be reported as positive, negative, or indeterminate and must be reviewed by an experienced TB specialist, radiologist, or a pulmonologist. If the assessment by IGRA is positive or indeterminate on retest, the study participant must undergo appropriate study-specified withdrawal procedures. The retest during Screening must be done during the protocol-defined Screening window.

10.7.9.6 TB assessment by chest x-ray

Chest radiographic imaging is done at Screening and results must be available at Baseline before first drug administration, unless a chest x-ray or CT is available within 2 months prior to Screening. The chest x-ray must be clear of signs of TB infection (previous or current) before first study medication administration. The chest x-ray should be repeated only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

The chest imaging must be negative for old or recent TB infection as determined by a qualified radiologist and/or pulmonary physician. Any new clinically significant findings post Baseline on chest x-ray must be documented in the source documents and the eCRF as an AE.

10.7.9.7 TB risk factors via the TB questionnaire

The TB questionnaire "Evaluation of signs and symptoms of tuberculosis" should be completed accurately and filed as a critical source document. The questionnaire will assist with the identification of study participants who may require therapy for TB. It will be completed as outlined in the schedule of assessments (Table 5-1).

A "Yes" response to any of the questions in the TB questionnaire during the study should trigger further assessments to determine if the study participant has either LTBI or active TB infection and must be withdrawn from the study (see below for details). As an example, a study participant who answers "Yes" at Screening to the question "Has the participant been in close (eg, sleeping in the same room) contact with an individual with active TB, or an individual who has recently been treated for TB?" should not be allowed in the study pending further assessments (including TB specialist consult) to determine if the study participant has either LTBI or active TB infection. In case of any doubt, UCB recommends seeking the opinion of a TB specialist before starting or continuing study medication intake.

10.7.9.8 TB management

For inclusion in the study, see Section 6.2 (Exclusion Criteria).

10.7.9.8.1 Latent TB, active TB, or other NTMB infection identified during study

During the study, study participants who develop evidence of LTBI, active TB, or NTMB infection must immediately stop further administration of study medication and will be referred to an appropriate TB specialist (pulmonologist or infectious disease specialist) for further evaluation and appropriate clinical management. Study participants must be withdrawn and scheduled to return for the Early Discontinuation Visit as soon as possible but no later than the next scheduled study visit and complete all Early Discontinuation Visit assessments. The study participant should be encouraged to complete the Final Visit (12 weeks after the last dose of IMP).

If infection with NTMB is identified during the study, the same procedure as for active TB acquired during the study and compliant TB treatment shall be followed.

10.7.9.8.2 Tuberculosis testing during the study for study participants above and below 5 years of age

Upon signing the updated Informed Consent form, all study participants need to undergo TB testing as described below.

Study participants above 5 years of age

IGRA testing (QuantiFERON) should be done once a year (approximately every 48 weeks) for all study participants from 5 to 17 years of age as described in Section 10.7.9.5.

Study participants below 5 years of age

At Screening, the TST and IGRA are both mandatory. Both these tests must be negative to be eligible for study inclusion (Note that some antihistaminics have the potential to interact with the TST response and render it negative). If either test is positive, the study participant should be referred to a TB specialist and the study participant must not initiate IMP. If the IGRA becomes positive during the study, the IMP administration must be stopped and study participants should be referred to TB specialist.

In countries with high BCG vaccination or high TST positivity, it is not recommended to do the TST. The TST may be positive due to BCG vaccination, however UCB will not permit enrollment of pediatric study participants <5 years of age into a study without written approval from a physician with expertise in pediatric TB.

IGRA testing (QuantiFERON) should be done once a year (approximately every 48 weeks) for all study participants below 5 years of age. There is currently no IGRA adapted to pediatrics in terms of blood volume required for the test (ie, no validated test performance with a smaller blood volume). Therefore, if a maximum cumulative blood draw volume is cited by an IRB/EC for a pediatric clinical study, exceptions may be made for other clinical lab assessments in order to accommodate the IGRA volume requirement.

11 ASSESSMENT OF EFFICACY AND HEALTH OUTCOMES VARIABLES

11.1 PedACR30, PedACR50, PedACR70, and PedACR90 clinical response

The PedACR30, PedACR50, PedACR70, and PedACR90 clinical responses rates (Giannini et al, 1997; Lovell et al, 2008) at every visit compared to Baseline (except the Final Visit) will be assessed. The assessments are based on a 30%, 50%, 70%, and 90% or greater improvement in at least 3 of the 6 core set measures with no more than 1 of the remaining worsened by >30%. The 6 core set measures are:

- Number of joints with active arthritis (joints with swelling not due to deformity or inactive synovitis, or joints with limitation of motion with pain, tenderness, or both)
- Number of joints with limitation of range of motion
- Physician's Global Assessment of Disease Activity (VAS)
- CHAQ completed by parent or caregiver (Appendix 17.1)
- Parent's Global Assessment of Overall Well-Being (VAS) (Appendix 17.3)
- Acute phase reactant (CRP)

Documentation of the assessment of all 6 core set measures will be submitted to UCB or designee for immediate review of completeness at Week 0 (Baseline) and Week 24, while the study participant is still on site.

11.2 PRINTO/PRCSG standard joint examination

The following 75 joints are to be examined for swelling, pain on motion (POM), tenderness, and limitation of motion (LOM) by the Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. Preferably the same assessor should evaluate the study participant at each arthritis assessment, as per PRINTO/PRCSG guidelines. The individual with this delegated duty must be listed on Form 1572.

- Upper body (6) - bilateral temporomandibular, sternoclavicular, and acromioclavicular joints
- Upper extremity (34) - bilateral shoulders, elbows, wrists, metacarpals (MCP I, II, III, IV, and V), proximal interphalangeals (PIP I, II, III, IV, and V) and distal interphalangeals (DIP II, III, IV, and V)
- Lower extremity (30) - bilateral hips, knees, ankles, subtalar, tarsi, metatarsophalangeals (MTP I, II, III, IV, and V), and proximal interphalangeals (PIP I, II, III, IV, and V)
- Spinal (5) – cervical spine, thoracic spine, and lumbar spine, and bilateral sacroiliac joints

The assessment for LOM is made on 69 joints from the above list. The sternoclavicular, acromioclavicular, and sacroiliac joints are excluded. The assessment for swelling is made on

66 joints from the above list. The hip, subtalar, cervical spine, thoracic spine, lumbar spine, and sacroiliac joints are excluded. Artificial and ankylosed joints are excluded from both tenderness and swelling assessments.

Joint assessment will be based on a 2-point scale as unaffected (Grade 0) and affected (Grade 1).

These assessments are completed at Screening, Baseline, and every visit (including Unscheduled Visits that are related to dose change) through the Early Discontinuation/End of Treatment Visit.

11.3 Number of joints with active arthritis and number of joints with limitation of range of motion

The change in the number of joints with active arthritis and the change in the number of joints with limitation of range of motion will be assessed. Joint and joint motion assessments will be performed as part of the PRINTO/PRCSG standard joint examination.

11.4 Physician's Global Assessment of Disease Activity (VAS)

The Investigator will assess the overall status of the study participant with respect to their JIA signs and symptoms and functional capacity using a 0 to 100mm VAS where 0 is "very good, asymptomatic and no limitation of normal activities" and 100 is "very poor, very severe symptoms which are intolerable and inability to carry out all normal activities."

The Physician's Global Assessment of Disease Activity (VAS) will be completed at Screening, Baseline, and every visit (including Unscheduled Visits that are related to dose change) through the Early Discontinuation/End of Treatment Visit.

11.5 Childhood Health Assessment Questionnaire (CHAQ)

The Childhood Health Assessment Questionnaire (CHAQ) is an adaptation of the Health Assessment Questionnaire-Disability Index (HAQ-DI), which is a questionnaire developed to assess physical function in adults (Singh et al, 1994). The CHAQ was developed specifically as a measure of function for children with juvenile RA and the population evaluated for the development of this questionnaire comprised study participants between ages 1 to 19 years old with JIA. The CHAQ is a parent/caregiver-reported questionnaire and the recall period is "the past week."

The disability section of the CHAQ uses 30 questions (5-point Likert scale) to assess 8 domains of daily living, namely dressing & grooming, arising, eating, walking, hygiene, reach, grip, and activities. In addition to the questions on activities of daily living, there are 14 questions relating to the use of aids or devices, and 8 questions concerning activities in which assistance of another person is required. The CHAQ for use in children differs from the HAQ-DI in that several new questions have been added such that for each functional area, there is at least 1 question that is relevant to children of all ages. Further, to eliminate discrepancies introduced by growth and development, parents/caregivers are asked to note only those difficulties that are caused by arthritis. The question with the highest score determines the score for that functional area. If aids or devices are used or help is needed to complete tasks in a certain area, a minimum score of 2 is recorded for the corresponding

functional area. The scores for each of the 8 functional areas or domains are averaged to calculate the Disability Index which yields a score of 0 representing "no disability" to 3 representing "very severe disability."

A copy of the CHAQ is provided in Appendix 17.1. The CHAQ will be completed by the parents/caregivers at Screening, Baseline, and every visit (including Unscheduled Visits that are related to dose change) through the Early Discontinuation/End of Treatment Visit. Preferably, the same parent/caregiver should complete the questionnaires for each visit. The questionnaire will not be collected if the study participant is not living with a parent/caregiver at least part-time, ie, if the parent/caregiver is not able to answer the questions appropriately. The questionnaire should be checked by site personnel for completeness.

11.6 Parent's Assessment of Arthritis Pain (VAS)

In the Parent's Assessment of Arthritis Pain (VAS), the parent/caregiver is asked the following question "How much pain do you think your child has had because of his or her illness in the past week?" The parent/caregiver should then place a mark on a 100mm horizontal line to indicate the severity of the pain. This VAS 100mm line has as anchors 0mm representing "No Pain" and 100mm, "Very Severe Pain."

The Parent's Assessment of Arthritis Pain (VAS) is provided in Appendix 17.2. The Pain (VAS) will be completed at Screening, Baseline, and every visit through the Early Discontinuation/End of Treatment Visit. Preferably, the same parent/caregiver should complete the scale for each visit. The scale will not be completed if the study participant is not living with a parent/caregiver at least part-time, ie, if the parent/caregiver is not able to answer the question appropriately. The scale should be checked by site personnel for completeness.

11.7 Parent's Global Assessment of Overall Well-Being (VAS)

In the Parent's Global Assessment of Overall Well-Being (VAS), the parent/caregiver is asked the following question "Considering all the ways that arthritis affects your child, rate how your child is doing on the following scale by placing a mark on the line." The parent/caregiver should then place a mark on a 100mm horizontal line ranging from 0 "Very well" to 100 "Very poor."

The Parent's Global Assessment of Overall Well-Being (VAS) is provided in Appendix 17.3. The Parent's Global Assessment of Overall Well-Being (VAS) will be completed at Screening, Baseline, and every visit (including Unscheduled Visits that are related to dose change) through the Early Discontinuation/End of Treatment Visit. Preferably, the same parent/caregiver should complete the scale for each visit. The scale will not be completed if the study participant is not living with a parent/caregiver at least part-time, ie, if the parent/caregiver is not able to answer the question appropriately. The scale should be checked by site personnel for completeness.

11.8 C-reactive protein (CRP)

The acute phase reactant CRP will be analyzed by the central laboratory. Samples will be collected at Screening, Baseline, and every visit (including Unscheduled Visits that are related to dose change) through the Early Discontinuation/End of Treatment Visit. Values

will be used in determining PedACR clinical response, JADAS, CID and CRM, and ratio to Baseline in CRP.

11.9 JADAS

The change in the JADAS from Baseline will be assessed. The JADAS-71 is a composite disease activity score based on a 71-joint count and includes the measures (normalized as needed): Physician's Global Assessment of Disease Activity (VAS) (0 to 10), the Parent's Global Assessment of Overall Well-Being (VAS) (0 to 10), the active joint count (0 to 71), and CRP (0 to 10) (Consolaro et al, 2009; Nordal et al, 2010).

The JADAS will be completed at Screening, Baseline, and every visit through the Early Discontinuation/End of Treatment Visit.

Values of CRP will be normalized to a 0 to 10 scale as follows: if CRP is expressed in mg/dl, any values above 10 are converted to 10. If expressed in mg/L, the value will be first divided by 10 and then any values above 10 will be converted to 10.

Values below the minimum threshold for the method used for CRP determination are converted to 0.

The JADAS is calculated as the linear sum of the scores of the 4 components with a total score range of 0 to 101.

11.10 Clinically Inactive Disease and clinical remission

Criteria for Clinically Inactive Disease (CID) are defined as follows (Wallace et al, 2011):

- No joints with active arthritis*
- No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA
- No active uveitis as defined by the Standardization of Uveitis Nomenclature Working Group**
- ESR or CRP within normal limits in the laboratory where tested or, if elevated, not attributable to JIA
- Physician's Global Assessment of Disease Activity score of best possible on the scale used (0mm on the 100mm VAS)
- Duration of morning stiffness of ≤15 minutes

All criteria must be met.

* Note: The American College of Rheumatology defines a joint with active arthritis as a joint with swelling not due to bony enlargement or, if no swelling is present, limitation of motion accompanied by either pain on motion and/or tenderness. An isolated finding of pain on motion, tenderness, or limitation of motion on joint examination may be present only if explained by either prior damage attributable to arthritis that is now considered inactive or nonrheumatologic reasons, such as trauma.

** Note: The Standardization of Uveitis Nomenclature Working Group defines inactive anterior uveitis as "grade zero cells," indicating <1 cell in field sizes of 1mm by a 1mm slit beam.

Clinical remission on medication (CRM) is defined as criteria for CID achieved for at least 6 continuous months (Wallace et al, 2004; Wallace et al, 2009).

Clinically Inactive Disease will be assessed at every post-Baseline visit except the Final Visit. Clinical remission on medication will be assessed at every post-Baseline visit from Week 24 onwards, except the Final Visit.

Study participants achieving CRM, ie, after 6 months of continuous CID, may discontinue CZP treatment at the Investigator's discretion following consultation with the Sponsor to confirm remission status. Study participants who have discontinued CZP due to achieving CRM will be allowed to remain in the study and continue with scheduled study visits. Study participants not maintaining persistent CID following achievement of CRM will be allowed to resume CZP treatment at any time at the Investigator's discretion and consultation with the Sponsor. If a study participant is on concomitant MTX treatment, the Investigator may decide to decrease and ultimately discontinue the MTX dose after complete discontinuation of CZP. Study participants not maintaining persistent CID following achievement of CRM and resuming treatment will restart the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a maintenance dose administered Q2W for the duration of the study, with exception of the lowest weight group on the reduced dose regimen, who will receive the maintenance dose Q4W.

11.11 Duration of morning stiffness (DMS)

Morning stiffness is defined by the time elapsed between the time of usual awakening (even if not in the morning) and the time the study participant is as limber as he/she will be during a day involving typical activities. The study participant/caregiver will be asked the following question (Kirwan and Reeback, 1986):

"How long does it take, from the time you (your child) wake up, for you (your child) to become as limber as you (your child) will be?"

For those experiencing relief, the actual hours elapsed should be recorded no matter how long. The duration in hours and minutes will be recorded. For those study participants with unrelenting stiffness, 24 hours should be recorded.

Duration of morning stiffness will be assessed at Baseline and at every visit through the Early Discontinuation/End of Treatment Visit.

11.12 Faces Pain Scale-Revised (FPS-R)

The Faces Pain Scale-Revised (FPS-R) is a self-reported measure used to assess the intensity of children's pain (Hicks et al, 2001). The original version of the scale consists of 7 faces increasing in pain intensity and approximating equal intervals as assessed by children (Bieri et al, 1990). Children have to select a level on the scale that matches their own pain. A numerical value is associated with the different levels on the scale. The FPS-R was adapted from the FPS in order to make scoring possible on the widely accepted 0 to 10 metric. It includes 6 faces (instead of 7). This tool has been validated for children aged 5 to 12 years

and will be assessed in children ages 5 to 11 years. Study participants enrolled at 5 to 11 years of age will continue with the FPS-R when reaching 12 years of age. Completion of the FPS-R will not be required for study participants enrolled at 2 to 4 years of age if they reach 5 years of age during the study.

The FPS-R is provided in Appendix 17.4. The FPS-R will be administered at Baseline and then daily during the first week of the study; at Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) through the Early Discontinuation/End of Treatment Visit. The questionnaire should be checked by site personnel for completeness.

11.13 Patient's Assessment of Arthritis Pain (JIA Pain VAS)

In the JIA Pain VAS, study participants aged 12 years or older are asked the following question "How much pain have you had because of your illness today (acute version)/in the past week (standard version)?" (as applicable). The study participant should then place a mark on a 100mm horizontal line to indicate the severity of the pain. This VAS 100mm line has as anchors 0mm representing "No Pain" and 100mm, "Very Severe Pain."

Both versions of the JIA Pain VAS are provided in Appendix 17.5 and Appendix 17.6. The Pain (VAS) will be completed at Baseline (acute and standard versions), daily during the first week of treatment (acute version); Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) through the Early Discontinuation/End of Treatment Visit (standard version). The scale should be checked by site personnel for completeness.

11.14 Fatigue Assessment Scale (NRS)

The study participant's level of tiredness (fatigue) will be assessed by the Fatigue Assessment Scale (numeric rating scale [NRS]) where the parent/caregiver are asked the following question:

"Please rate your child's fatigue (weariness, tiredness) during the past week on a scale of 0 to 10" where 0 is "No fatigue" and 10 is "Fatigue as bad as you can imagine."

The recall period for this instrument is the past week.

The Fatigue Assessment Scale is provided in Appendix 17.7. The Fatigue Assessment Scale will be assessed at Baseline, Weeks 1, 2, 4, 8, and then every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) and the Early Discontinuation/End of Treatment Visit. Preferably, the same parent/caregiver should complete the scale for each visit. The scale will not be completed if the study participant is not living with a parent/caregiver at least part-time, ie, the parent/caregiver is not able to answer the question appropriately. The scale should be checked by site personnel for completeness.

11.15 Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey

The Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey is a parent/caregiver-reported self-administered questionnaire, which captures information related to the impact of the disease on the child's ability to participate in school and social/after-school activities and evaluate the impact of disease on the parent or caregiver's productivity at their paid work and in the household. The same parent/caregiver should complete the questionnaire at each visit. The recall period, for the questions relating to the child's school attendance and parent/caregiver's work productivity, is the past 4 weeks. This survey collects information related to eg, the child's attendance to school, number of school days missed due to the disease, number of school days impacted due to the disease, level of difficulty in performing school activities, the parent or caregiver's employment status, number of days missed from work due to the child's disease, number of days with work productivity reduced by half or more due to child's disease, days with no household work due to child's disease, days with productivity within household reduced by half or more due to child's disease. For further information please see the instructions provided on the worksheet.

The Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey (parent/caregiver) will be assessed at Baseline, Week 4 and every visit through the Early Discontinuation/End of Treatment Visit. The full questionnaire and instructions are provided in Appendix 17.8.

12 STUDY MANAGEMENT AND ADMINISTRATION

12.1 Adherence to protocol

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator may use his/her medical judgment and may remove a study participant from immediate hazard before notifying UCB (or its representative) and the IRB/IEC in writing regarding the type of emergency and the course of action taken.

12.2 Monitoring

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

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

The Investigator will allow UCB (or designee) to periodically review all CRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of CRFs, ensure that

all protocol requirements, applicable authorities regulations and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

12.2.1 Definition of source data

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

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

Some data will be recorded directly in the CRF and will not appear in a source document as defined in the Source Data Verification (SDV) form.

Source documents that are computer-generated and stored electronically do not need to be printed if the electronic medical record system at the investigational site is 21CFR Part 11 compliant. If the system is not 21CFR Part 11 compliant, the source data must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the study participant's source documents. The Investigator will authorize the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records such as Holter monitor records or electroencephalogram records must be saved and stored as instructed by UCB (or designee).

12.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, study participant files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes).

The procedures for conducting SDV on computerized study participant records (if the system is 21CFR Part 11 compliant) are the same as those for paper records. Source data verification is performed by reviewing the electronic record directly.

All data reported on the CRF should be supported by source documents, unless otherwise specified in Section 12.2.1.

12.3 Data handling

12.3.1 Case report form completion

This study will use RDC. The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the electronic CRFs and in all required reports.

Any change or correction to the CRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) must be reapproved by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the electronic CRF.

Detailed instructions will be provided in the CRF Completion Guidelines.

12.3.2 Database entry and reconciliation

Case report forms/external electronic data will be entered/loaded in a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data are entered into the electronic CRFs once and are subsequently verified.

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

12.3.3 Study participant screening and enrollment log/Study participant identification code list

The study participant's screening and enrollment will be recorded in the study participant screening and enrollment log.

The Investigator will keep a study participant identification code list. This list remains with the Investigator and is used for unambiguous identification of each study participant.

The study participant's consent and enrollment in the study must be recorded in the study participant's medical record. These data should identify the study and document the dates of the study participant's participation.

12.4 Termination of the study

A futility analysis of the PedACR30 response rate was performed after all active study participants on the reduced CZP dose had completed the Week 16 (Visit 8) assessments. If less than 50% of the study population enrolled on the reduced CZP dose regimen (Protocol Amendment 5) achieved a PedACR30 response at Week 16, the study was to be discontinued. The futility analysis confirmed that ≥50% of the study population enrolled on the reduced CZP dose regimen achieved a PedACR30 response at Week 16. A further futility analysis will not be performed using the additional participants that will be enrolled on the original CZP dose regimen following the implementation of Protocol Amendment 9.

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused investigational products and other material in accordance with UCB procedures for the study.

12.5 Archiving and data retention

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

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period; however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (ICH-GCP Guideline, Section 4.9.5). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's study master file.

12.6 Audit and inspection

The Investigator will permit study-related audits mandated by UCB 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 study participants enrolled have been protected, that enrolled study participants (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH/GCP, and applicable regulatory requirements.

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

12.7 Good Clinical Practice

Noncompliance with the protocol, ICH/GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

13 STATISTICS

A description of statistical methods is presented below and will be described in more detail in the Statistical Analysis Plan (SAP). Any deviations from the final SAP, as well as changes from the protocol, will be detailed in the Clinical Study Report.

13.1 Definition of analysis sets

- The Enrolled Set (ES) will consist of all study participants who have given informed consent.
- The Safety Set (SS) will consist of all study participants in the ES who have received at least 1 dose of study medication.
- The Full Analysis Set (FAS) will consist of all study participants in the SS who have a valid Baseline and valid post-Baseline efficacy measurement.
- The Pharmacokinetic Per-Protocol (PK-PP) Population is a subset of the SS consisting of those study participants who took at least 1 dose of study medication, provided measurable plasma samples (with recorded sampling time) on at least 1 occasion and who had no important protocol deviations affecting the PK parameters, as confirmed during a preanalysis review prior to locking the database. This population will be used for the PopPK model and for all presentations of plasma concentration and PK data.
- The Pharmacokinetic-Pharmacodynamic (PK-PD) Population will consist of all study participants in the SS who have at least 1 post-Baseline plasma concentration measurement and 1 post-Baseline PedACR30 assessment.

13.2 General statistical considerations

The Baseline value is defined as the last nonmissing pretreatment measurement.

13.2.1 Data presentation

For safety and efficacy analyses, study participants will be grouped by their Baseline weight strata (10 to <20kg [22 to <44lb], 20 to <40kg [44 to <88lb], and ≥40kg [≥88lb]). Selected analyses will also group study participants by their Baseline age group, concomitant MTX use, and anti-CZP antibody status. Subgroups defined by CZP dosing regimen will also be displayed. Two CZP dosing regimen subgroups will be defined as follows:

- Original CZP dose regimen: includes all study participants in the SS who began treatment in accordance with the original dosing regimen defined for the study (3 loading doses of CZP at Weeks 0, 2, and 4 [minimum=100mg Q2W, maximum=400mg Q2W] followed by a maintenance dose for the duration of the study [minimum=50mg Q2W, maximum=200mg Q2W]). This subgroup includes all study participants who began the

study with this CZP dose regimen and received 1 or more doses of this regimen, regardless of any subsequent switch to the reduced CZP dose regimen.

- Reduced CZP dose regimen: includes all study participants in the SS who began treatment in accordance with the reduced dosing regimen defined for the study (3 loading doses of CZP at Weeks 0, 2, and 4 [minimum=50mg Q2W, maximum=200mg Q2W] followed by a maintenance dose for the duration of the study [minimum=50mg Q4W, maximum=100mg Q2W]). This subgroup includes all study participants who began the study with this CZP dose regimen and received 1 or more doses of this regimen, regardless of any subsequent switch to the original CZP dose regimen.

Summary statistics will consist of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation, minimum and maximum) will be presented.

For those parameters likely to have a skewed distribution (eg, CRP), geometric means with associated coefficients of variation and/or quartiles may be presented.

13.2.2 Multicenter studies

Approximately 55 centers are planned to enroll the original 156 study participants into this study. A subset of these centers will be used to enroll the additional 30 study participants following Protocol Amendment 9. The enrollment per site is limited to a maximum of 12 study participants.

13.2.3 Coding dictionaries

Medications will be coded with the World Health Organization Drug Dictionary and AEs will be coded according to MedDRA®. In both cases, the version used will be that current to the Sponsor at the time of data capture.

13.3 Planned safety analyses

The incidence of serious TEAEs and TEAEs leading to permanent withdrawal of IMP will be assessed as primary safety variables in this study. Other safety variables include the incidence of TEAEs, TEAEs of interest, TEAEs by relatedness, TEAEs by severity, and TEAEs by duration of exposure. The primary summaries of safety will include all study participants in the SS, regardless of CZP dose. Safety variables will be summarized overall and separately for the 2 CZP dose regimens (original CZP dose regimen, reduced CZP dose regimen).

Safety summaries will include presentations of AEs, extent of exposure, laboratory values (hematology and biochemistry), vital signs, concomitant medications and procedures, and autoantibody (ANA and anti-dsDNA antibodies) concentrations. Urinalysis results will be listed. Tanner stages will be presented by category. Growth as measured by height and weight will be assessed in relation to a comparative population and this may include an assessment of any change after treatment with CZP.

For AEs, the exposure-adjusted incidence rate (EAIR) will also be calculated. For EAIR, the numerator will be the total number of study participants experiencing a particular AE. The denominator will be study participant-years, ie, the total summation of individual study participant-years at risk up to the first occurrence of the given AE for study participants with

that AE, plus the total study participant-years at risk for those study participants not experiencing that AE.

For the original CZP dose regimen subgroup, in addition to the overall presentation of AEs, AEs will be summarized separately for the periods of exposure to original CZP dose regimen and the reduced CZP dose regimen, in addition to exposure for study participants that switched from the reduced CZP dose regimen to the original CZP dose regimen following Protocol Amendment 9. Additionally, the frequency and percentage of AEs reported during the first 16 weeks of study medication exposure will be summarized separately for the 2 CZP dose regimens (original CZP dose regimen, reduced CZP dose regimen). This analysis will be repeated, excluding any study participants who switched from the original to the reduced CZP dose regimen prior to Week 16. Selected safety summaries will be presented overall and by Baseline weight strata, as well as by age (2 to 5 years, 6 to 11 years, and 12 to 17 years), by concomitant MTX use, and by anti-CZP antibody status.

13.4 Planned PK, PD, and immunological variable analysis

Certolizumab pegol plasma concentrations levels at Week 16 and Week 48 will be assessed as primary variables in this study. Other PK and immunological variables include CZP plasma concentrations at other study timepoints and anti-CZP antibody levels throughout the study.

Plasma CZP concentrations will be used to build a PopPK model with the nonlinear mixed-effect modeling (NONMEM) software. The model will be parameterized in terms of clearance, volume of distribution, and absorption rate constant. Details of the PopPK modeling procedures will be described in a separate data analysis plan. The pediatric PopPK model will be combined with PD data (PedACR) and if the data allow, an exposure response relationship will be derived. These modeling analyses and results will be reported separately.

All study participants enrolled following Protocol Amendment 9 will have plasma CZP concentrations and anti-CZP antibodies analyzed using the ECLIA method. In addition, PK and ADA samples (for which sufficient volume is available) collected in this study prior to Protocol Amendment 9 will be analyzed with the ECLIA method.

Data from the ECLIA method will constitute the study's main PK and anti-CZP antibody evaluations. As such, PK and anti-CZP antibody data generated with the original ELISA method will be reported as Listings. Plasma CZP concentration data generated by the ECLIA method will be tabulated and summarized (geometric mean, arithmetic mean, minimum, maximum, standard deviation and % coefficient of variation) by study dose regimen (original CZP dose regimen or reduced CZP dose regimen) for each PK sampling visit. Plasma concentration time curves will be plotted, along with respective individual anti-CZP antibody titers where available, separately for study participants who began treatment according to the original CZP dose regimen or the reduced CZP dose regimen, overall, and by Baseline age stratum. Subgroup analyses will include study participants enrolled with Protocol Amendment 9 and those treated up to the Week 16 timepoint under the original maintenance dosing regimen. Where available, individual ECLIA-based anti-CZP antibody data will be tabulated by study visit and Baseline age stratum (all study participants, 2 to 5 years, 6 to

11 years, and 12 to 17 years). In addition, safety and efficacy profiles by antibody titers (or titer categories) may be investigated.

In addition, the effect of concomitant use of MTX versus monotherapy on CZP plasma concentration and incidence of anti-CZP antibodies will be evaluated.

13.5 Planned efficacy and health outcomes analyses

Summary statistics will be presented for efficacy and health outcomes variables using the FAS.

All efficacy and health outcomes variables results will be presented overall and separately for the 2 CZP dose regimens (original CZP dose regimen, reduced CZP dose regimen).

The following efficacy variables are defined as secondary variables in this study:

- PedACR30, PedACR50, PedACR70, and PedACR90 response rates at Week 16 as compared to Baseline.

The following efficacy variables are defined as other variables:

- PedACR30, PedACR50, PedACR70, and PedACR90 response rates at every visit except Week 16 and Final Visit as compared to Baseline.

For PedACR30, PedACR50, PedACR70, and PedACR90, results will be presented overall and by Baseline weight strata, as well as by age (2 to 5 years, 6 to 11 years, and 12 to 17 years), by concomitant MTX use, and by anti-CZP antibody status.

- Change from Baseline in number of joints with active arthritis at every visit except Final Visit.
- Change from Baseline in number of joints with limitation of range of motion at every visit except Final Visit.
- Change from Baseline in Physician's Global Assessment of Disease Activity (VAS) at every visit except Final Visit.
- Change from Baseline in CHAQ at every visit except Final Visit.
- Change from Baseline in Parent's Assessment of Arthritis Pain (VAS) at every visit except Final Visit.
- Change from Baseline in Parent's Global Assessment of Overall Well-Being (VAS) at every visit except Final Visit.
- Ratio to Baseline in CRP at every visit except Final Visit.
- Change from Baseline in JADAS at every visit except Final Visit. The JADAS is a composite disease activity score including the Physician's Global Assessment of Disease Activity, the Parent's Global Assessment of Overall Well-Being, the active joint count, and CRP.
- Percentage of study participants with Clinically Inactive Disease (CID), as defined in Section 11.10, at every post-Baseline visit except Final Visit.

- Percentage of study participants with clinical remission on medication (CRM), as defined in Section 11.10, at every post-Baseline visit from Week 24 onwards except Final Visit.
- Time (in days) to CID.
- Time (in days) to CRM.
- Change from Baseline in DMS at every visit except Final Visit.
- Change from Baseline on FPS-R (child-reported, for study participants ages 5 to 11 years), daily during the first 7 days of treatment; Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) through the Early Discontinuation/End of Treatment Visit.
- Change from Baseline in JIA Pain VAS, daily during the first week of the study (acute and standard versions); Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) through the Early Discontinuation/End of Treatment Visit (standard version) for study participants ages 12 to 17 years.
- Change from Baseline in Fatigue Assessment Scale at every visit except Weeks 12 and 20, and Final Visit.
- Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey responses at Baseline, Week 4, and every visit thereafter except Final Visit.

13.6 Handling of dropouts or missing data

For all binary efficacy endpoints assessing response, study participants who withdraw early will be considered as non-responders from that time point onwards. The exception is efficacy data for study participants who withdraw after Week 56: Per Protocol Amendment 7, these will not be imputed (as nonresponse or missing) and will be analyzed as observed.

For continuous efficacy endpoints, missing assessments will be imputed using the last observation carried forward (LOCF) approach. These summaries will be supported by observed case (OC) analyses. Per Protocol Amendment 7, missing assessments after Week 56 will no longer be imputed and will be analyzed as observed.

Data collected after the taking of rescue medication will be treated as missing for continuous efficacy endpoints and non-response for binary efficacy endpoints in all analyses except where specifically stated otherwise. See Section 7.8.2 for a list of medications which would result in data at only the next scheduled visit (and not all subsequent visits) being treated as missing/non-response. These data will then be imputed as for any other missing data. The exception is any rescue medication use that is initiated after Week 56: Per Protocol Amendment 7, efficacy data after any rescue medication use initiated after Week 56 will not be imputed (as nonresponse or missing) and will be analyzed as observed.

Missing or partial dates for safety evaluations will be imputed and full details of these algorithms will be presented in the SAP.

As discussed in Section 13.2, Baseline is defined as the last nonmissing pretreatment measurement, therefore if available, data from the Screening visit will be used as Baseline values, if these data are missing at Week 0.

No further imputations of any other missing data are planned (eg, efficacy data missing at random [MAR]).

13.7 Interim analysis and data monitoring

A futility analysis of the PedACR30 response rate was performed after all active study participants enrolled on the reduced CZP dose had completed the Week 16 (Visit 8) assessments. If less than 50% of the study population enrolled on the reduced CZP dose regimen (Protocol Amendment 5) achieved a PedACR30 response at Week 16, the study was to be discontinued. The futility analysis confirmed that ≥50% of the study population enrolled on the reduced CZP dose regimen achieved a PedACR30 response at Week 16. Given the descriptive nature of the data presentations, there were no statistical implications of this interim analysis. A further futility analysis will not be performed using the additional study participants that will be enrolled on the original CZP dose regimen following the implementation of Protocol Amendment 9.

In addition to the futility analysis, several interim analyses were planned, including interim analyses of PK data, and full interim analyses of PK, immunogenicity, safety, and efficacy endpoints, as described below.

Interim analyses of PK data

Per original protocol, if the pediatric plasma concentrations demonstrate that the geometric mean and median concentrations are below the adult 5th percentile or above the 95th percentile, the PK data will be used to re-evaluate the weight-based dose adjustment algorithm for pediatric study participants. Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future interim analyses, which may include PopPK, indicate that plasma concentrations of JIA study participants are outside of the exposure range observed in previous adult RA studies, a revised pediatric dose algorithm will be derived. Any change in dose regimen will require a protocol amendment prior to implementation.

An interim analysis of PK data conducted following Protocol Amendment 3 compared CZP plasma concentration data from this study with CZP plasma concentrations observed previously in adult study participants with RA. Interim analysis of CZP plasma concentrations was started when 6 study participants in 1 of the age groups completed Week 12 (Visit 7). Comparisons were made between the Week 12 geometric mean and median values for the pediatric and adult study participants, as well as between the individual pediatric data and the adult 5th and 95th percentile and minimum and maximum observed values.

Based on results of this interim PopPK analysis (also described in Section 5.1), the dosing regimen was changed with Protocol Amendments 4 and 5, and the doses to be administered were reduced by 50% for all weight groups. This change was intended to achieve plasma

concentrations similar to the effective concentrations observed in previous studies in adult study participants with RA.

Interim analyses of PK, immunogenicity, safety, and efficacy endpoints

An interim analysis of PK, immunogenicity, safety, and efficacy endpoints was performed after all active study participants that were enrolled and treated prior to implementation of Protocol Amendment 9 had completed the Week 24 (Visit 10) assessments, and the results were reported separately. An interim analysis, including all enrolled participants, for all PK, immunogenicity, safety, and efficacy endpoints will be performed after all active study participants, including those enrolled following the implementation of Protocol Amendment 9, have completed the Week 24 (Visit 10) assessments.

Further interim analyses may be performed at the Sponsor's discretion as required.

A DSMB will periodically review emerging safety and efficacy data. The DSMB members will be independent of the Sponsor and Investigators. The DSMB members will be informed by the Patient Safety representative (or designee) of all SAEs at the time of expedited reporting and will periodically review emerging safety data (eg, SAEs, AEs, safety laboratory data) and efficacy data, as applicable, during the course of the study. Based on the safety data, the DSMB can recommend modifying/stopping the study.

13.8 Determination of sample size

Based upon the ICH guideline for the assessment of safety, it is planned to enroll a sufficient number of study participants to this study to have a minimum of 100 with at least 12 months continuous exposure to CZP. Assuming a dropout rate of approximately 20%, it was originally determined that 125 study participants would need to be enrolled. At the time of Protocol Amendment 5, 78 study participants had been enrolled according to the original CZP dose regimen, and it was planned to enroll a further 78 study participants on the reduced CZP dose regimen, so that a comparable number of study participants on the reduced CZP dose regimens could be analyzed. Thus, the total number of study participants planned to be enrolled was increased to 156 study participants. Assuming a Screening failure rate of 25%, it is planned to screen 195 study participants in total.

With Protocol Amendment 9, an additional 30 study participants will be enrolled on the original dose regimen with the aim to enroll at least 5 study participants in each weight range of 10 to <20kg (22 to <44lb), 20 to <40kg (44 to <88lb), and ≥40kg (≥88lb).

Prior to the start of study conduct, simulations using the adult population PK model in pediatric study participants with JIA suggested that the planned sample size of 125 study participants was adequate for PK assessment purposes. Individual apparent clearance (CL/F) and volume of distribution (V/F) were simulated for a total of 125 study participants (using the same approach presented in C87079 report addendum 08 Oct 2008 performed for 190 study participants). In all age groups, the standard errors of both PK parameters, CL/F and V/F, relative to their mean were substantially <20%, with values ranging from 5.5 to 7.0% for CL/F and from 4.6 to 7.5% for V/F. A tabular summary of the results is presented below.

Table 13-1 PK simulation results for 125-study participant study sample size

Parameter	Age group (years)	Mean	Standard error	Standard error/ Mean (%)
CL/F	4 to 8	0.253	0.015	6.0
	9 to 12	0.356	0.025	7.0
	13 to 17	0.432	0.024	5.5
V/F	4 to 8	2.90	0.134	4.6
	9 to 12	4.80	0.358	7.5
	13 to 17	6.80	0.334	4.9

CL/F=apparent clearance; PK=pharmacokinetic; V/F=apparent volume of distribution

Data from all 186 study participants will be included in the final PopPK analysis, and therefore should allow CL/F and V/F to be determined with sufficient precision.

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Informed consent

Adequate information will be provided to the study participant and his/her parent(s)/legally acceptable representative(s) in both oral and written form and consent will be obtained in writing prior to performance of any study specific procedure. The content and process of obtaining informed consent will be in accordance with all applicable regulatory and IRB/IEC requirements.

All IRBs which oversee US research must be registered with the FDA.

UCB will provide a sample informed consent form, child assent form, and study participant information sheet. The final consent form must be approved by the IRB/IEC and should contain the applicable ICH-GCP elements in a language readily understood by the study participant (ie, lay terminology).

If the informed consent form is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended informed consent form by the IRB/IEC and use of the amended form.

For the US sites a Health Insurance Portability and Accountability Act (HIPAA) agreement will be provided if required by the IRB or institution.

The Investigator or designee should fully inform the study participant about all pertinent aspects of the study including the fact that the protocol has been granted the approval of the IRB/IEC and local regulatory authorities if required.

Study participants and their parent(s)/legally acceptable representative(s) will be informed of the purpose of the study in unambiguous language they easily understand. Their participation is voluntary and they can at any time decide to stop their participation without any influence on their future care or treatment. The study participants and their parent(s)/legally acceptable representative(s) must be informed about the main procedures used to guarantee their anonymity, especially during the analysis of their personal data. Study participants and their parent(s)/legally acceptable representative(s) should be able to ask any questions about the study and to receive relevant answers.

After having received extensive information about the purpose and risks of the study and having had enough time to consider participation in the study, the study participant's parent(s)/ legally acceptable representative(s) or legal guardian must give their written consent by signing and dating the Informed Consent Form. This form will also be signed and dated by the person who obtained the informed consent and then retained by the Investigator. If applicable, a child assent form may be used. This form will also be dated and signed by the study participant and by the person who obtained the child assent and then retained by the Investigator. Obtaining of consent (and child assent, where applicable) will be confirmed in the study participant's medical records. The study participant's parent(s)/legally acceptable representative(s) will receive a copy of the signed and dated consent form (and child assent, where applicable) and the original will be filed in the Investigator's Study File.

The study participants and their parent(s)/legally acceptable representative(s) may withdraw their consent to participate in the study at any time. A study participant is considered as enrolled in the study when his/her parent(s)/legally acceptable representative(s) has signed the informed consent form (and child assent, where applicable). A CRF must not be started, nor may any study specific procedure be performed for a given study participant, without having obtained his/her parent's or legally acceptable representative's written consent to participate in the study.

If any new information that could influence the study participant's decision to stay in the study becomes available, this information will be transmitted to the study participant's parent(s)/legally acceptable representative(s) without delay. In addition, the informed consent form (and child assent form where applicable) must be amended accordingly or a separate consent form (and child assent form where applicable) be created and submitted to the IRB/IEC for approval prior to being implemented for reconsent (and child assent) of all ongoing study participants in the study and for use in obtaining consent from all parent(s)/legally acceptable representative(s) of study participants (and child assent) who enter the study from that point forward.

Adequate information will be provided to the study participant and his/her parent(s)/legally acceptable representative(s) in both oral and written form and consent (and child assent) will be obtained in writing prior to performance of any study specific procedure. The content and process of obtaining informed consent (and child assent) will be in accordance with all applicable regulatory and IRB/IEC requirements.

14.2 Study participant identification cards

Upon signing the informed consent form and child assent form (as applicable), the study participant or legal representative will be provided with a study participant identification card in the language of the study participant. The Investigator will fill in the name of the study and medical emergency contact information. The Investigator will instruct the study participant/legal representative to keep the card with them at all times.

14.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, informed consent form, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other study participant-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human study participants or others, and any protocol deviations, to eliminate immediate hazards to study participants.

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the study participants. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on the Committee's requirements), at intervals appropriate to the degree of study participant risk involved but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators, in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

14.4 Study participant privacy

UCB staff (or designee) will affirm and uphold the study participant's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the study participant number assigned at Screening.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the study participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge

summaries for hospital admissions occurring during a study participant's study participation, and autopsy reports for deaths occurring during the study).

14.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

15 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

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

16 REFERENCES

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17 APPENDICES

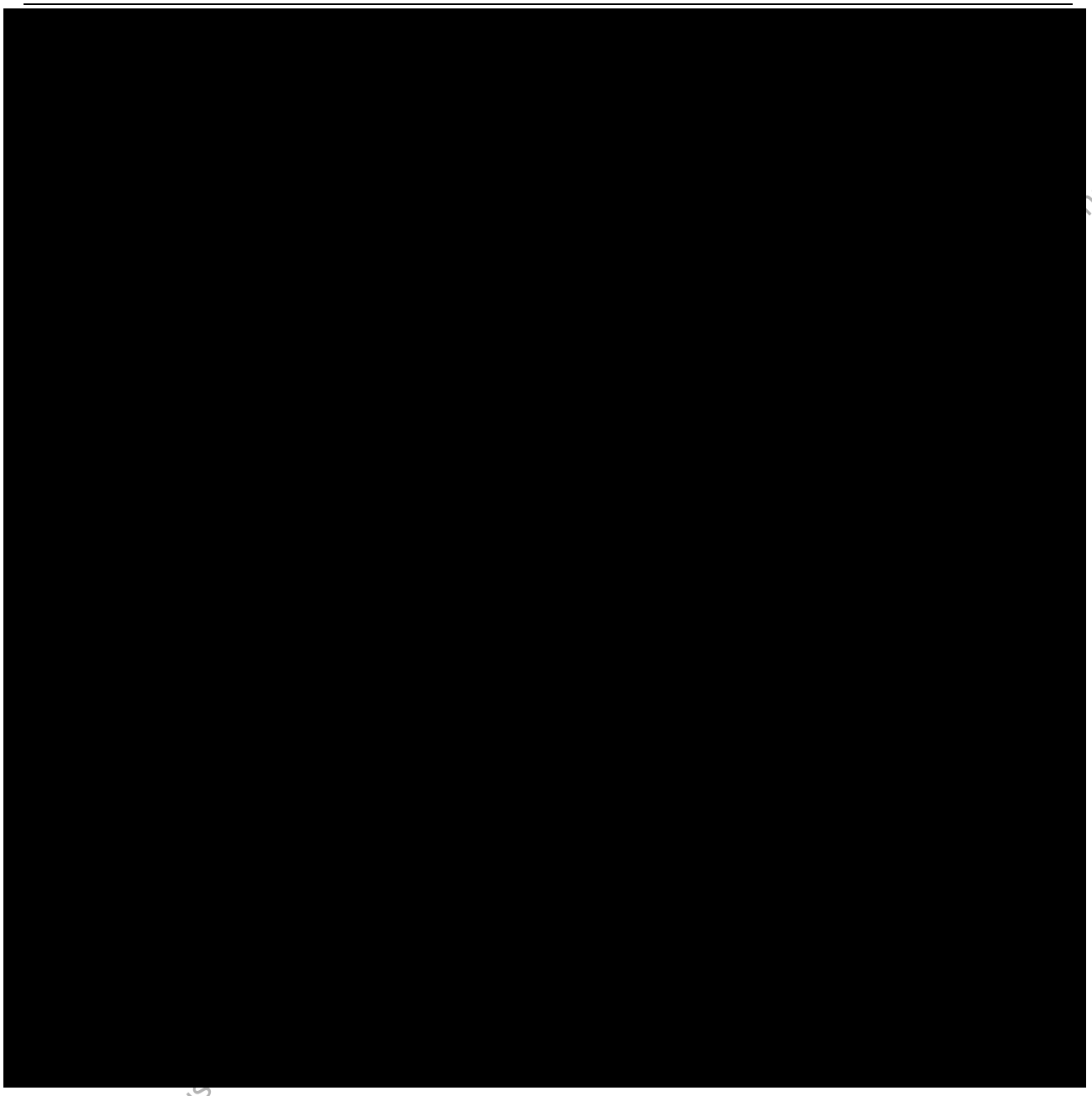
Scales in the appendix are intended for information only and are not to be copied for use in data collection. The actual CRF page may differ in format or presentation from what is contained in the protocol appendix.

17.1 Childhood Health Assessment Questionnaire (CHAQ)

1 **CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE**

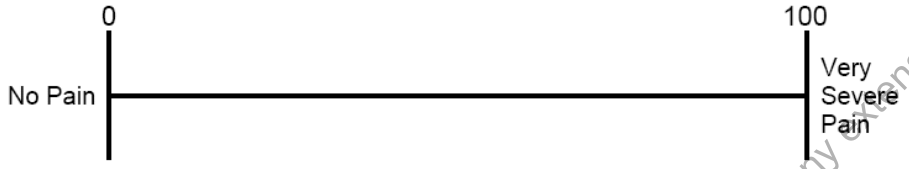
2

In this section we are interested in learning how your child's illness affects his/her ability to function in daily life. Please feel free to add any comments on the back of this page. In the following questions, please check the one response which best describes your child's usual activities (averaged over an entire day) **OVER THE PAST WEEK. ONLY NOTE THOSE DIFFICULTIES OR LIMITATIONS WHICH ARE DUE TO ILLNESS**. If most children at your child's age are not expected to do a certain activity, please mark it as "Not Applicable". **For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young but not because he/she is RESTRICTED BY ILLNESS, please mark it as "NOT Applicable".**



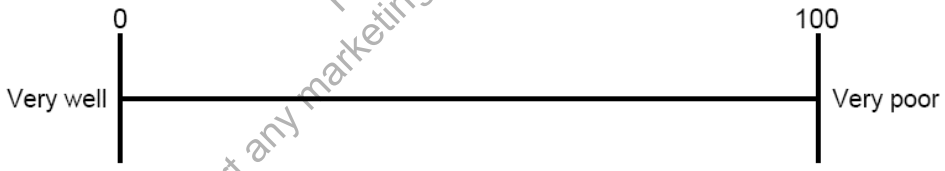
17.2 Parent's Assessment of Arthritis Pain (VAS)

How much pain do you think your child has had because of his or her illness IN THE PAST WEEK? Please mark on the line below to indicate the severity of the pain.



17.3 Parent's Global Assessment of Overall Well-Being (VAS)

Considering all the ways that arthritis affects your child, rate how your child is doing on the following scale by placing a mark on the line.



17.4 Faces Pain Scale-Revised

Faces Pain Scale – Revised (FPS-R)

www.painsourcebook.ca
Version: 18 Oct 2009 CL von Baeyer

In the following instructions, say "hurt" or "pain", whichever seems right for a particular child.

"These faces show how much something can hurt. This face *[point to left-most face]* **shows no pain** [hurt]**. The faces show more and more pain** *[point to each from left to right]* **up to this one** *[point to right-most face]* **- it shows very much pain** [hurt]**. Point to the face that shows how much you hurt** [right now]**."**

*Score the chosen face **0**, **2**, **4**, **6**, **8**, or **10**, counting left to right, so "0" = "no pain" and "10" = "very much pain". Do not use words like "happy" and "sad". This scale is intended to measure how children feel inside, not how their face looks.*

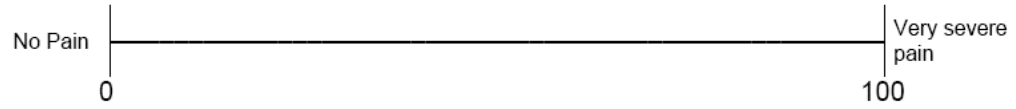
Sources. Hicks CL, von Baeyer CL, Spafford P, van Korlaar I, Goodenough B. The Faces Pain Scale - Revised: Toward a common metric in pediatric pain measurement. *Pain* 2001; 93:173-183. Bieri D, Reeve R, Champion GD, Addicoat L, Ziegler J. The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: Development, initial validation and preliminary investigation for ratio scale properties. *Pain* 1990; 41:139-150.

10 8 6 Fold here 4 2 0

FPS-R_US and Canada_English_Final_5 Aug 2010

17.5 Patient's Assessment of Arthritis Pain (JIA Pain VAS, acute version)

How much pain have you had because of your illness TODAY?
Place a mark on the line below to indicate the severity of the pain.



17.6 Patient's Assessment of Arthritis Pain (JIA Pain VAS, standard version)

How much pain have you had because of your illness IN THE PAST WEEK?
Place a mark on the line below to indicate the severity of the pain.

17.7 Fatigue Assessment Scale (NRS)

Please rate your child's 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**

17.8 Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey

Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey

Self-Administered Questionnaire

The purpose of this questionnaire is to understand the impact of the child's arthritis on school (for the child) and work activities (for the parents/caregivers). There is a series of questions that are asked of the parent or caregiver who comes with the child to the clinic for the visits associated with this study. The questions are either multiple choice (in which case, you should select the one best answer) or you are asked to estimate a quantity, such as school days missed (in which case, a number is to be entered). If the child with arthritis is not attending school, the school-related questions should be skipped and the rest of the questionnaire should be completed. If the parent/caregiver is not employed at a paid job, only the section about paid work should be skipped; the rest of the questionnaire should be completed.

We are interested in adult responses, so if another child (an older sibling, for example) is involved in providing care, but they are less than 18 years old, please do not record answers for that person.

Some of the questions may seem like they have been asked more than once. Nevertheless, please respond as best you can to each question. The information will be collected at multiple visits throughout the study. **The same parent/caregiver should complete the questionnaires for each visit.**

1. Please indicate which parent or caregiver is completing this questionnaire. (Please check only ONE box.)

   ☐ Mother
   ☐ Father
   ☐ Stepmother
   ☐ Stepfather
   ☐ Other caregiver (please specify) _____

2. In general, which adult provides MOST of the day-to-day care for the child with arthritis? (Please check only ONE box.)

   ☐ Mother
   ☐ Father
   ☐ Stepmother
   ☐ Stepfather
   ☐ Both parents provide the care about equally
   ☐ Other adult caregiver (please specify)_____

3. How many adults live with the child with arthritis in the household **and** provide care to the child? (That is, would take time away from work or other activities to take care of the child, provide transportation to visit doctors or therapists, obtain medication, give medication to the child, etc.)

   ☐ 1
   ☐ 2
   ☐ 3
   ☐ 4
   ☐ More than 4

4. Is there any outside help that is used to provide care and support for the child with arthritis (that is, adults who don't live with the child, but would help take care of the child, take the child to appointments, give medication to the child, etc.) such as relatives, friends, nannies, etc.?

   ☐ No, there is no outside help at all
   ☐ Yes, there is unpaid outside help (relatives, friends, etc.)
   ☐ Yes, there is paid outside help (nannies, maids, etc.)
   ☐ Yes, there is a combination of paid and unpaid outside help

5. If there is outside help, about how many **hours per week** is help received from adults who don't live with the child with arthritis?

   _____ Hours per week

Arthritis and School

6. In the **past four weeks**, has the child with arthritis attended school?

   ☐ Yes. **Please answer questions 7-12.**

   ☐ No → If NO, indicate why the child was not in school.
   - ☐ Not old enough to go to school
   - ☐ Child is home schooled
   - ☐ Does not go to school because of arthritis
   - ☐ School was not in session (holiday, summer break, etc.)
   - ☐ Child has completed school
   - ☐ Other (please specify)_____

*If the child with arthritis is **not attending** school, please **go to question 13**, "Arthritis and Impact on Work" questions.*

7. How many days in the **past four weeks** has school been in session for the child with arthritis? (For example, if they usually attend school Monday – Friday, record 20 school days in the past four weeks. If the child had a school holiday one day, record 19 school days in the past four weeks. If the child attends school 6 days a week, and had no holidays, please write down 24 days.)

   _____ **Days of school**

8. In the **past four weeks**, how many **full days** of school did the child with arthritis miss **because of arthritis**? Please do not count visits associated with this study. *If none, please write 0.*

   _____ **Full days of school missed**

9. In the **past four weeks**, how many days did the child with arthritis **go to school late or leave school early** because of their arthritis? (For example, because they had a medical appointment, were not feeling well, had physical therapy, etc.) Do not count the full days of school that the child may have missed. *If none, please write 0.*

   _____ **Days when child arrived late or left early because of arthritis**

10. In the **past four weeks, while the child with arthritis was at school**, how much difficulty did they have at school because of their arthritis? (For example, participating in activities, interacting with others, completing assignments, etc.)

    ☐ No difficulty
    ☐ Mild difficulty
    ☐ Moderate difficulty
    ☐ Severe difficulty
    ☐ Complete difficulty

11. In the **past four weeks, while the child with arthritis was at school**, did the child have to **modify or miss** a gym or physical education class because of their arthritis?

- ☐ Child did not attend gym class because of their arthritis
- ☐ Yes, gym class was modified because of arthritis
- ☐ Yes, gym class was sometimes missed because of arthritis
- ☐ No, child attended gym class normally
- ☐ Child did not attend gym class for other reasons

12. In the **past four weeks, while the child with arthritis was at school**, how much of the time did they have to modify their writing activities because of arthritis? (For example, allow for more time to complete tests or written assignments, have assistance with completing assignments, etc.)

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

Arthritis and Impact on Work

13. In the table below, please check the box that indicates the current employment status of the adult caregivers who are most responsible for providing support to the child with arthritis.

One caregiver can respond for multiple caregivers. For example, if the mother is completing the questionnaire, she can respond for herself and also indicate whether the father is employed. If a certain caregiver type does not apply in this situation (for example, there are no step parents), please check the "Not Applicable" box.

Caregiver	Current Employment Status				
	Employed full-time	Employed part-time	Not employed due to child's arthritis	Not employed for other reasons	Not Applicable
Mother	☐	☐	☐	☐	☐
Father	☐	☐	☐	☐	☐
Stepmother	☐	☐	☐	☐	☐
Stepfather	☐	☐	☐	☐	☐
Other adult caregiver (please specify) _____	☐	☐	☐	☐	☐

The table below is meant to capture the impact of a child's arthritis on the caregivers' work at both paid and household jobs. The caregiver(s) may be the mother, father and/or another caregiver.

Please provide information only for the caregiver or caregivers who are at the clinic with the child with arthritis, even if that caregiver is not the one who provides most of the care to the child. For example, if both the father and mother are present, please fill in the columns for each of them. If only one caregiver is present, please complete only one column and leave the other columns blank. If the caregiver present is not the father or the mother, please specify who the caregiver is and complete the third column. If more than one caregiver is present, and neither of the caregivers is the mother or father, please record responses for the one caregiver who provides most of the care to the child with arthritis.

Complete questions 14-17 for the caregiver, whether employed or not.			
	Mother	Father	Other caregiver (please specify) _____
14. How many **full days** in the **past four weeks** did you not do **household** work because of the child's arthritis? (For example, because of appointments, providing medical assistance, providing transportation to school or medical appointments, physical therapy, etc.) Please do not count visits associated with this study. *If none, please write 0.*	____ Days	____ Days	____ Days
15. How many days in the **past four weeks** was your productivity in **household** work reduced by half or more because of the child's arthritis? (For example, because of appointments, providing medical assistance, providing transportation to school or medical appointments, physical therapy, etc.) *Do not include full days counted in question 14.* Please do not count visits associated with this study. *If none, please write 0.*	____ Days	____ Days	____ Days
16. How many days in the **past four weeks** did you miss **family, social or leisure** activities because of the child's arthritis? Please do not count visits associated with this study. *If none, please write 0.*	____ Days	____ Days	____ Days
17. In the **past four weeks**, how much has the child's arthritis interfered with your **household work** productivity on a scale of 0-10, where 0 = "no interference" and 10 = "complete interference"?			
Complete items 18-20 ONLY if the caregiver is employed at a paid job.			
18. In the **past four weeks**, how many full days of **work** have you had to miss because of the child's arthritis? (For example, due to appointments, providing medical assistance, providing transportation to school or medical appointments, physical therapy, etc.) Please do not count visits associated with this study. *If none, please write 0.*	____ Days	____ Days	____ Days
19. How many days in the **past four weeks** was your productivity at **work** reduced by half or more because of the child's arthritis? (For example, because of appointments, providing medical assistance, providing transportation to school or medical appointments, physical therapy, etc.) Do not include days counted in question 18. Please do not count visits associated with this study. *If none, please write 0.*	____ Days	____ Days	____ Days
20. In the **past four weeks**, how much has the child's arthritis interfered with your **work** productivity (work outside of home) on a scale of 0-10, where 0 = "no interference" and 10 = "complete interference"?			

17.9 TB questionnaire

Tuberculosis Worksheet (Source)

Evaluation for signs and symptoms of tuberculosis questionnaire

This worksheet was completed for the: ☐ **Subject** ☐ **Caregiver, name:** _____

The following questions are to be asked of every subject/caregiver for evaluation of risk factors for tuberculosis (TB). Responses to each question must be documented on this source document.

• Has the subject/caregiver been in close contact (i.e., sharing the same household or other enclosed environment) with an individual with active TB or an individual who has recently been treated for TB?	☐ Yes	☐ No
• Does the subject/caregiver have a new cough lasting more than 14 days or a change in a chronic cough?	☐ Yes	☐ No
• Does the subject/caregiver have night sweats?	☐ Yes	☐ No
• Does the subject/caregiver have a persistent fever?	☐ Yes	☐ No
• Does the subject/caregiver have unintentional weight loss (more than 10% of body weight)?	☐ Yes	☐ No
• Is the subject/caregiver a hospital employee or in frequent contact with hospital employees (example: providing catering service to hospital employees or married to one)?	☐ Yes	☐ No
• Is the subject/caregiver frequently exposed to other subjects (study visits/ hospitalizations) that are on study drug or other immunosuppressive drugs?	☐ Yes	☐ No
• Does the subject/caregiver reside in, did the subject/caregiver ever reside in, or is the subject/caregiver frequently traveling to a TB endemic region(s)?	☐ Yes	☐ No
• Does the subject/caregiver reside in, did the subject/caregiver ever reside in, or is the subject/caregiver frequently visiting densely populated areas such as highly urbanized city centers?	☐ Yes	☐ No
• Does the subject/caregiver frequently use public transportation?	☐ Yes	☐ No
• Is the subject/caregiver in frequent contact with elderly or underprivileged populations (homeless or other people needing social assistance)?	☐ Yes	☐ No
• Does the subject/caregiver appear malnourished?	☐ Yes	☐ No
• Has the subject/caregiver had an abnormal chest x-ray since the last evaluation?	☐ Yes	☐ No

04 May 2010 *(v.2009-10-22)*

17.10 Liver Safety – Suggested Actions and Follow-up Assessments

17.10.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.4, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as AEs and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 10.3), and, if applicable, also reported as an SAE (see Section 10.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 17–1 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 17.10.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 17.10.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Table 17–1 summarizes the approach to investigate PDILI.

Table 17–1: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms [a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN [b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and participant discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 17.10.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥8xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation - immediate IMP discontinuation not required (see Section 17.10.1.2).	Not required unless otherwise medically indicated (at discretion of investigator).	
≥5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 17.10.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the participant also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 17.10.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

17.10.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the participant must be discussed with the Medical Monitor as soon as possible. If required, the participant must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 17.10.1.3) and SAE report (if applicable).

17.10.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.4 and Table 17–1 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

17.10.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 17–2 (laboratory measurements) and Table 17–3 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding eCRFs. If the medical history of the participant indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible.

The following measurements are to be assessed:

Table 17–2: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR [a]
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

[a] Measured only for participants with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 17–3: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

17.10.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 17–1. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

17.11 Protocol Amendment 1

The version of the protocol dated 14 Jan 2010 was submitted to FDA on 28 Jan 2010. This version has not been submitted to any other regulatory authorities, IRBs/IECs, or Investigators. Therefore the integrated protocol contains only the rationale for the amendment and a general summary of changes. The detailed changes to the protocol dated 14 Jan 2010 are available upon request.

Rationale for the amendment

The primary purpose of this substantial protocol amendment is to revise the protocol in line with change requests from health authorities following discussions on the CZP pediatric arthritis development program.

In addition, a list of anticipated SAEs for CZP in the JIA population was added based on the FDA Final Rule on safety reporting for IND studies.

Further key revisions include updates of eligibility criteria, update of the protocol to current terminology used in the rheumatology community and to current company standards, and clarification of assessments and concomitant medications. In addition, administrative and editorial changes were made to update study personnel, rearrange the schedule of study assessments to group related assessments, and correct typographical errors.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- The Sponsor name has been changed from “SCHWARZ BIOSCIENCES GmbH – A Member of the UCB Group of Companies” to “UCB BIOSCIENCES GmbH.”
- The assessments of vital signs and laboratory parameters previously included in the primary safety variable have been redefined as “other” safety variables. The primary safety variable is the incidence of AEs.
- The assessment of the effectiveness of CZP on the clinical response in children and adolescents with moderate to severe polyarticular-course JIA was added as a secondary objective.
- In line with the change above, a few efficacy variables formerly listed as “exploratory” have been redefined as “secondary” (PedACR30, PedACR50, PedACR70, and PedACR90 response rates at Week 16) or “other” variables (all other efficacy variables).
- An additional study objective has been added to reflect the “other” variables.
- The study population was further defined to include study participants with polyarticular-course JIA except systemic JIA. In addition, the term “polyarticular-course JIA” for the studied indication replaces “polyarticular JIA.”
- The study population was further defined to include a minimum number of study participants in each body weight and age class, to include a minimum number of study

participants with ERA, and to include a minimum number of study participants who receive CZP as monotherapy.

- The exclusion criteria have been reordered to group arthritis-related criteria and medical history-related criteria.
- Text describing planned interim analyses has been updated to reflect full interim analyses at Week 16 and Week 56, instead of Week 24.
- A study stopping rule has been added, stating that the study will be discontinued if less than 50% of the study population achieves PedACR30 response at Week 16.
- For the comparison of PK data with previously observed plasma concentrations from adult study participants with RA, at least 20 study participants instead of 15 study participants (minimum of 6 instead of 4 study participants in each age group) are required to have completed Week 12 (Visit 7).
- The protocol has been updated with current terminology used in the rheumatology community with regard to "Clinically Inactive Disease (CID)" and "clinical remission."
- "Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey" replaces "productivity measure."
- The Patient's Assessment of Arthritis Pain questionnaire ("How much pain have you had because of your illness today/in the past week?") has been separated into an acute version, which will be used daily during the first week of treatment ("How much pain have you had because of your illness today?") and a standard version ("How much pain have you had because of your illness in the past week?").
- The following assessments have been removed throughout the protocol: erythrocyte sedimentation rate, respiration rate, thyroid function, and rheumatoid factor.
- "Tanner stage (pubertal maturity only)" has been changed to "Tanner stages (except growth)" for clarity.

17.12 Protocol Amendment 2

Rationale for the amendment

The primary purpose of this **administrative** amendment is to reflect a change in the participating countries, including removal of Western Europe. RA0043 will not be included in the European Paediatric Investigational Plan and will therefore not be conducted in Western Europe.

In addition, study personnel and the phone contact information for SAE reporting were updated.

The format and style of the document was changed to comply with UCB's new document authoring software; these changes are not specifically noted.

Modifications and changes

Specific changes

This section displays the modifications in this amendment compared with the previous version of the protocol dated 26 Aug 2011. The changes are displayed in the order of appearance.

Change #1

Under SPONSOR DECLARATION, the name of the Clinical Program Director:

[redacted]

Has been changed to:

[redacted]

Change #2

Under STUDY CONTACT INFORMATION, the name and contact details of the Clinical Program Director:

Clinical Program Director

Name:	[redacted]
Address:	1950 Lake Park Drive Smyrna, GA 30080 USA
Phone:	[redacted]

Have been changed to:

Clinical Program Director

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

Change #3

Under SERIOUS ADVERSE EVENT REPORTING, the phone contact information for SAE reporting (24h) and safety related issues:

• **Phone**	**Europe and Rest of the World:** +32 2 386 24 68 **USA & Canada:** +1 678 799 4007

Has been changed to:

• **Phone**	**Europe, USA & Canada, and Rest of the World:** +32 2 386 24 68

Change #4

Section 5.1.3 Anticipated regions and countries:

The regions planned for participation in this study are North America and Western Europe, with possible extension to other regions.

Has been changed to:

The regions planned for participation in this study are North and South America and Russia, with possible extension to other regions.

Change #5

Section 5.4.1 Study design, the last sentence of the first paragraph has been removed:

In addition, the study is proposed to fulfill the requirements for a pediatric investigation plan in compliance with the European pediatric regulation, with the objective to develop and make CZP available in the pediatric JIA population in the EU.

17.13 Protocol Amendment 3

Rationale for the amendment

The primary purpose of this substantial amendment is to update the exclusion criteria and guidelines related to TB detection and monitoring in order to comply with the revised UCB TB Task Force policy applied to all UCB-sponsored studies that include study participants with immunological diseases, who are at risk of developing or reactivation of TB infection, which might be associated with the class of anti-TNF blockers including the investigational drug. These instructions are evidence-based and reflect the updated recommendations of various national guidelines (eg, CDC diagnosis of latent TB infection, http://www.cdc.gov/TB/topic/testing/default.htm). This guideline includes the preference of use of PPD testing over IGRA in children below the age of 5 years. With the implementation of Protocol Amendment 3, PPD testing will be mandatory for study participants from 2 to 4 years of age in this study, unless the study participant has received a BCG vaccination, and IGRA testing will be required for study participants from 5 to 17 years of age.

In addition, the assessment of vital signs (especially the measurement of blood pressure) was adapted to the current UCB standard of safety assessment for CZP studies, in order to follow a consistent process in the collection of safety data across the UCB development program, and lactate dehydrogenase was added to complete the panel of laboratory parameters.

A DSMB will be implemented to conform with the standards for pediatric clinical studies. The DSMB will review emerging safety data from the study and will replace the study-specific Safety Review Committee. Activities will be defined in the DSMB charter.

Furthermore, this substantial amendment introduces a full interim analysis at Week 24 involving a complete data analysis for the inclusion in the marketing application for the JIA indication. At the same time, the planned analysis at Week 16 has been reduced to an analysis of the PedACR30 response rate required to confirm adequate response of the study population to CZP treatment and to confirm continuation of RA0043.

Key revisions also include modifications of the following eligibility criteria:

- Eligibility criteria related to the diagnosis of JIA (inclusion criterion 6) have been revised for clarity.
- Use of DMARDS and MTX (inclusion criteria 8 and 9) has been revised for clarity.
- TB exclusion criteria (exclusion criterion 11 and withdrawal criteria 3 and 4) have been updated to comply with the revised UCB policy.
- Exclusion criterion 13 (hepatitis screening panel) has been revised for clarity.
- Follow-up period for pregnancy and contraception (exclusion criteria 16 and 17) has been adapted to allow for compliance with local requirements.
- An exclusion criterion for infections (exclusion criterion 25) has been added.

In addition, the Per Protocol Set was deleted given that efficacy variables are secondary in this study, and an additional PK-PD Population was defined.

Further revisions were made to clarify study-related procedures (eg, the process of analyzing CZP plasma concentrations in the first cohort of study participants and the completion of parent-reported questionnaires), to clarify the CZP assay methodology, and to correct errors in the previous protocol version (eg, in relation to the components of the PedACR). In addition, the definition of the Physician's Global Assessment criterion for CID and CRM was changed to conform with the most current standard as defined by Wallace et al (2011).

The sentence that the pediatric PopPK model may be combined with PD data (PedACR) for an exposure response relationship has been moved from the variables section into the section on the assessment of pharmacokinetics and immunological variables as it represents an analysis rather than a variable.

References to the findings of the interim analysis of plasma concentration data from the clinical study of CZP in children and adolescents with Crohn's disease (C87035) have been removed from the protocol because of the differences between C87035 and the present study (ie, differences in dose interval and potential for impact of disease characteristics on clearance), and in consideration of the more relevant plan for an interim analysis of plasma concentration data from the present study in children and adolescents with JIA, as described in this protocol.

The reference to the JADAS has been changed from "JADAS-75" to "JADAS" and it has been clarified that for the purpose of this study, 71 joints will be included in the analysis in line with the PRINTO/PRCSG joint assessment used in this study.

In addition, administrative and editorial changes have been made, eg, to update study personnel and correct typographical errors.

Modifications and changes

Global changes

The following changes have been made throughout the protocol:

- All procedures related to TB detection and monitoring have been updated in order to comply with the revised UCB TB Task Force policy and company-wide recommendations that are based on international guidelines. This applies to eligibility criteria, withdrawal criteria, and timing and descriptions of related assessments throughout the protocol. In the tabular schedule of study assessments and the description of study procedures by visit, TB-related assessments have been grouped for clarity.
- References to the findings of an interim analysis of plasma concentration data from C87035 in children and adolescents with Crohn's disease have been removed throughout the protocol.
- "Study participant and parent/caregiver" has been added throughout the "Study procedures by visit" section for the TB questionnaire. This global change is not listed under the specific changes.
- The following terminology changes have been made throughout the protocol; these global changes are not listed under the specific changes:
  - "QuantiFERON" has been replaced by "IGRA" in line with the updated TB policy.

- The reference to the JADAS has been changed from "JADAS-75" to "JADAS" throughout the protocol.
- "IVRS phone call" has been changed to "IXRS contact" to account for the use of an interactive voice/web response system.
- References to Global Clinical Safety and Pharmacovigilance (GCSP) have been changed to "Drug Safety."

Specific changes

This section displays the modifications in this amendment compared with the previous version of the protocol dated 02 Jul 2012. The changes are displayed in the order of appearance.

Change #1

On the SPONSOR DECLARATION page, the name of the Clinical Trial Biostatistician:

[redacted]

Has been changed to:

[redacted]

Change #2

On the SPONSOR DECLARATION page, the name of the Clinical Program Director:

[redacted]

Has been changed to:

[redacted]

Change #3

Under STUDY CONTACT INFORMATION, the name and contact details of the Clinical Program Director:

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

Have been changed to:

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

Change #4

Under STUDY CONTACT INFORMATION, the name and contact details of the Clinical Trial Biostatistician:

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

Have been changed to:

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

Change #5

Under STUDY CONTACT INFORMATION, the name of the Medical Monitor Europe:

Name:	[redacted]
Phone:	
Fax:	

Has been changed to:

Name:	[redacted]
Phone:	
Fax:	

Change #6

Under SERIOUS ADVERSE EVENT REPORTING, the contact details:

Serious Adverse Event reporting (24h) and safety related issues	
• **Fax**	**Europe and Rest of the World:** +32 2 386 24 21 **USA:** +1 800 880 6949 **Canada:** +1 877 582 8842
• **Phone**	**Europe, USA & Canada, and Rest of the World:** +32 2 386 24 68

Have been changed to:

Serious adverse event reporting (24h)	
• **Fax**	**Europe and Rest of the World:** +32 2 386 24 21 **USA:** +1 800 880 6949 **Canada:** +1 877 582 8842
• **E-mail**	**Global:** DS_ICT@ucb.com

Change #7

LIST OF ABBREVIATIONS, the following abbreviations have been added:

CDC	Centers for Disease Control and Prevention
DSMB	Data and Safety Monitoring Board
IBD	inflammatory bowel disease
IGRA	interferon-gamma release assay
IXRS	interactive voice/web response system
LTB	latent tuberculosis
NTMB	nontuberculous mycobacteria
PK-PD	Pharmacokinetic-Pharmacodynamic
SDV	source data verification

Change #8

LIST OF ABBREVIATIONS, the following abbreviations have been removed:

GCSP	Global Clinical Safety and Pharmacovigilance
IVRS	interactive voice response system
PPS	Per Protocol Set

Change #9

Section 1 Summary, third paragraph, the second sentence:

Study participants must have had polyarticular-course JIA for at least 6 months prior to Baseline.

Has been changed to:

Study participants must have had onset of signs and symptoms consistent with polyarticular-course JIA and initiation of JIA treatment for at least 6 months prior to Baseline.

Change #10

Section 1 Summary, the following has been added below the fifth paragraph:

An interim analysis of the American College of Rheumatology Pediatric 30% (PedACR30) response rate will be performed after all active study participants have completed the Week 16 (Visit 8) assessments. The study will be discontinued if less than 50% of the study population achieves a PedACR30 response at Week 16.

Change #11

Section 1 Summary, the seventh paragraph:

Full interim analyses will be performed after all active study participants have completed the Week 16 (Visit 8) assessments and after all active study participants have completed the Week 56 (Visit 14) assessments.

Has been changed to:

Full interim analyses will be performed after all active study participants have completed the Week 24 (Visit 10) assessments, as well as after all active study participants have completed the Week 56 (Visit 14) assessments. The study will continue until the approval of the marketing application for the polyarticular-course JIA indication in the study participant's country or region, or until discontinuation of the study based on the Week 16 analysis of response, or until further notice from UCB.

Change #12

Section 1 Summary, the following sentence has been moved from the seventh paragraph to the new text below the fifth paragraph:

The study will be discontinued if less than 50% of the study population achieves at least an American College of Rheumatology 30% (PedACR30) response rate at Week 16.

Change #13

Section 1 Summary, the eighth paragraph:

Certolizumab pegol will be administered as a fixed dose based on weight every 2 weeks (Q2W) throughout the study consisting of 3 loading doses at Weeks 0, 2, and 4 (minimum=100mg, maximum=400mg) followed by a treatment dose (minimum=50mg, maximum=200mg). Once at least 20 study participants (minimum 6 study participants in each age group: 2 to 5 years, 6 to 11 years, and 12 to 17 years) have completed Week 12

(Visit 7), PK data will be compared with plasma concentrations observed previously in studies conducted in adult study participants with rheumatoid arthritis (RA). Interim data from an ongoing clinical study in children and adolescents with Crohn's disease (ages 6 to 17 years) confirm that the weight-based dose adjustment for pediatric study participants with Crohn's disease leads to similar plasma concentrations as observed previously in adult study participants with Crohn's disease. However, if plasma levels of JIA study participants are not consistent with those observed in previous adult RA studies, the dosing algorithm may be changed via a protocol amendment.

Has been changed to:

Certolizumab pegol will be administered as a fixed dose based on weight every 2 weeks (Q2W) throughout the study consisting of 3 loading doses at Weeks 0, 2, and 4 (minimum=100mg, maximum=400mg) followed by a treatment dose (minimum=50mg, maximum=200mg). Interim analysis of PK data will compare plasma concentration data from this study with CZP plasma concentrations observed previously in adult study participants with rheumatoid arthritis (RA). This CZP plasma concentration analysis will be done on an ongoing basis throughout the study, starting when 6 study participants in 1 of the age groups have completed Week 12 (Visit 7). Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicate that no change to the dosing algorithm is required. If future analyses indicate that plasma levels of JIA study participants are outside of the exposure range observed in previous adult RA studies, the dosing algorithm may be changed via a protocol amendment.

Change #14

Section 1 Summary, last paragraph, the second sentence:

Other exploratory efficacy and health outcomes variables include: …

Has been changed to:

Other efficacy and health outcomes variables include: …

Change #15

Section 1 Summary, last paragraph, the following variable has been removed:

Shifts by visit of CRP from Baseline

Change #16

Section 1 Summary, last paragraph, the following variable:

Number of study participants meeting criteria of Clinically Inactive Disease (CID) and clinical remission on medication (CRM)

Has been changed to:

Percentage of study participants meeting criteria of Clinically Inactive Disease (CID) and clinical remission on medication (CRM)

Change #17

Section 2 Introduction, the first sentence:

Certolizumab pegol (CDP870, CZP, Cimzia®) is approved in the United States of America (USA), the European Union, and a number of other countries worldwide for the treatment of moderate to severe active RA in adults.

Has been changed to:

Certolizumab pegol (CDP870, CZP, Cimzia®) is approved in the United States of America (USA), the European Union, and a number of other countries worldwide for the treatment of moderately to severely active RA in adults.

Change #18

Section 2 Introduction, 13th paragraph, the first sentence:

In a placebo-controlled clinical study of study participants with RA, no difference was detected in antibody response to vaccine between CZP and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with CZP.

Has been changed to:

In a placebo-controlled clinical study of study participants with RA, no meaningful difference was detected in antibody response to vaccine between CZP and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with CZP.

Change #19

Section 4.3 Other variables, the following has been removed at the beginning of the section:

Other pharmacodynamic (PD) variables are:

- The pediatric PopPK model will be combined with PD data (PedACR) and if the data allow, an exposure response relationship will be derived.

Change #20

Section 4.3 Other variables, under "Other efficacy and health outcomes variables," the ninth bullet has been removed:

- Shifts by visit of CRP from Baseline.

Change #21

Section 5.1 Study description, the fourth and fifth paragraphs:

Full interim analyses will be performed:

- After all active study participants have completed the Week 16 (Visit 8) assessments
- After all active study participants have completed the Week 56 (Visit 14) assessments

If less than 50% of the study population achieves at least PedACR30 response at Week 16, the study will be discontinued.

Have been changed to:

An interim analysis of PedACR30 response rates will be performed after all active study participants have completed the Week 16 (Visit 8) assessments. If less than 50% of the study population achieves a PedACR30 response at Week 16, the study will be discontinued.

Full interim analyses will be performed:

- After all active study participants have completed the Week 24 (Visit 10) assessments
- After all active study participants have completed the Week 56 (Visit 14) assessments

Change #22

Section 5.1 Study description, the last 3 paragraphs:

Once at least 20 study participants (minimum 6 study participants in each age group: 2 to 5 years, 6 to 11 years, and 12 to 17 years) have completed Week 12 (Visit 7), PK data will be compared with plasma concentrations observed previously in adult study participants with RA.

This CZP plasma concentration analysis may be done in 2 or 3 stages if at least 20 study participants in total complete Week 12 (Visit 7) before 6 study participants in 1 or both of the other age groups have completed. The plasma concentration analysis would be performed on the available completed study participants in the first stage. The analysis would then be performed on the other age groups once the required minimum number of 6 study participants have completed Week 12 (Visit 7).

The therapeutic plasma concentration of CZP in children and adolescents is expected to be similar to that required for the adult population (see Section 5.4.2). If plasma concentrations are not consistent with those observed in previous studies with adults, the dosing algorithm may be changed via a protocol amendment. This study will continue during the PK analysis. All study participants assessed in this analysis will continue treatment after Week 12 (Visit 7).

Have been changed to:

Interim analysis of PK data will compare CZP plasma concentration data from this study with plasma concentrations observed previously in adult study participants with RA. This plasma concentration analysis will be done on an ongoing basis throughout the study, starting when 6 study participants in 1 of the age groups have completed Week 12 (Visit 7).

The therapeutic plasma concentration of CZP in children and adolescents is expected to be similar to that required for the adult population (see Section 5.4.2). Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicate that no change to the dosing algorithm is required. If future analyses indicate that plasma concentrations are outside of the exposure range observed in previous studies with adults, the dosing algorithm may be changed via a protocol amendment. This study will continue during the PK analysis.

All study participants assessed in this analysis will continue treatment after Week 12 (Visit 7).

Change #23

Section 5.1.1 Study duration by study participant, the last line:

Planned Last Study participant, First Visit – 2Q 2013

Has been changed to:

Planned Last Study participant, First Visit – 3Q/4Q 2013

Change #24

Section 5.1.2 Planned number of study participants and sites, the first sentence:

Approximately 167 study participants will be screened at about 70 centers in order to enroll 125 study participants in this study.

Has been changed to:

Approximately 167 study participants will be screened at about 55 centers in order to enroll 125 study participants in this study.

Change #25

Section 5.2 Schedule of study assessments, Table 5-1, Week 17 with footnote "u" has been added in the second header row, sixth column:

Study period	Screening	Baseline							
Week	-4 to 0[a]	0	1	2	4, 8, 12, 16, (17[u]), 20, 24	32 and every 8 weeks thereafter	Unsch. Visit[b]	Early Disc/ End of Treatment	Final Visit[c]

Change #26

Section 5.2 Schedule of study assessments, Table 5-1, the row for "TB questionnaire" has been moved below the row for "TB screening."

Change #27

Section 5.2 Schedule of study assessments, Table 5-1, the row "TB screening":

Study period	Screening	Baseline							
Week	-4 to 0[a]	0	1	2	4, 8, 12, 16, 20, 24	32 and every 8 weeks thereafter	Unsch. Visit[b]	Early Disc/ End of Treatment	Final Visit[c]
Visit (+/-3 days)[a]	1	2	3	4	5 to 10	11 onwards			FV
TB screening[n]	X					X[o]			

Has been changed to:

Study period	Screening	Baseline							
Week	-4 to 0[a]	0	1	2	4, 8, 12, 16, 17[u], 20, 24	32 and every 8 weeks thereafter	Unsch. Visit[b]	Early Disc/ End of Treatment	Final Visit[c]
Visit (+/-3 days)[a]	1	2	3	4	5 to 10	11 onwards			FV
TB screening[n] and chest x-ray[o]	X								

Change #28

Section 5.2 Schedule of study assessments, footnote "a" in Table 5-1:

[a] Screening Visit must be completed at least 4 days prior to the Baseline Visit. For all other visits, the Visit window is ±3 days relative to Baseline.

Has been changed to:

[a] Screening Visit must be completed at least 4 to 12 working days prior to the Baseline Visit, depending on regional requirements and laboratory assessments required for the study participant (please refer to Section 10.6 and the laboratory manual). For all other visits, the Visit window is ±3 days relative to Baseline.

Change #29

Section 5.2 Schedule of study assessments, footnote "d" in Table 5-1:

[d] Pulse, systolic/diastolic blood pressure, and temperature to be measured within approximately 15 minutes prior to dosing.

Has been changed to:

[d] Pulse, systolic/diastolic blood pressure, and temperature to be measured within approximately 15 minutes prior to dosing and in addition (pulse and blood pressure only) approximately 30 minutes after dosing.

Change #30

Section 5.2 Schedule of study assessments, footnotes "i," "j," and "k" in Table 5-1:

i TB questionnaire to be completed at Weeks 12 and 24, every 16 weeks thereafter, and Early Discontinuation/End of Treatment.
j Analyses will be performed by a central laboratory. Study participants do not have to be fasting.
k At Screening, laboratory testing includes testing for HBcAb, HBsAb, HBsAg, and HCVAb. In addition, HBV DNA is required for study participants with only positive HBcAb (negative HBsAg and HBsAb) or with only positive HBsAg. Rescreening on 1 additional occasion within the Screening Period is allowed after consultation with the Medical Monitor in case of isolated exclusionary laboratory results, if, in the Investigator's opinion, the value is not reflective of the study participant's previous clinical and laboratory pattern. In addition, retesting within the Screening Period is allowed after consultation with the Medical Monitor in case of reporting failure of laboratory results (eg, issues with transportation of samples).

Have been changed to:

i TB questionnaire to be completed at Weeks 12 and 24, every 16 weeks thereafter, and Early Discontinuation/End of Treatment. If the Investigator suspects reactivation of TB or active TB, TB testing and/or a chest x-ray should be performed.
j Analyses will be performed by a central laboratory, except urine dipsticks, which will be done locally at the site. Study participants do not have to be fasting.
k At Screening, laboratory testing includes testing for HBcAb, HBsAb, HBsAg, and HCVAb. In addition, HBV DNA is required for study participants with only positive HBcAb (negative HBsAg and HBsAb) or with only positive HBsAg. Retesting on 1 additional occasion within the Screening Period is allowed in case of isolated exclusionary laboratory results, if, in the Investigator's opinion, the value is not reflective of the study participant's previous clinical and laboratory pattern. In addition, retesting within the Screening Period is allowed in case of reporting failure of laboratory results (eg, issues with transportation of samples).

Change #31

Section 5.2 Schedule of study assessments, footnotes "m," "n," and "o" in Table 5-1:

[m] Pregnancy testing for postmenarcheal female study participants. Serum testing by a central laboratory at Screening and urine testing at Baseline, Weeks 8, 16, 24, and every visit thereafter.

[n] Performed ≤3 months within Screening. PPD tests should be read by a trained health care worker between 48 and 72 hours after injection. QuantiFERON testing is required to be performed by the central lab if the study participant has a documented history of severe positive PPD reaction or a documented history of Bacille Calmette-Guérin (BCG) vaccination.

[o] TB screening to be done at Week 48 and yearly (every 48 weeks) thereafter.

Have been changed to:

[m] Pregnancy testing for postmenarcheal female study participants. Serum testing by a central laboratory at Screening and urine testing locally at the site at Baseline, Weeks 8, 16, 24, and every visit thereafter.

[n] TB screening if not performed within 3 months of Screening: Interferon-gamma release assay (IGRA) testing (QuantiFERON®) is required to be performed by the central lab for all study participants from 5 to 17 years of age. PPD testing is mandatory for study participants from 2 to 4 years of age in this study unless written documentation of BCG vaccination is available (refer to Section 6.2 [exclusion criterion 11] and Section 10.7.9).

[o] A chest radiograph (anterior-posterior view at minimum, but preferably anterior-posterior and lateral) must be taken if the study participant has a positive IGRA/PPD testing at Screening or, if written documentation of BCG vaccination is available for study participants ages 2 to 4 years, a TB questionnaire indicating an increased study participant's risk of exposure or infection with TB. If a study participant has had a recent radiograph of the chest within approximately 3 months prior to Screening, it may be used in lieu of the protocol-required radiograph. All chest imaging must be read by a qualified radiologist/pulmonary physician who is specifically required to look for evidence of active TB or inactive TB. Refer to Section 10.7.9.2.1 for further information on chest x-rays.

Change #32

Section 5.2 Schedule of study assessments, footnote "u" in Table 5-1:

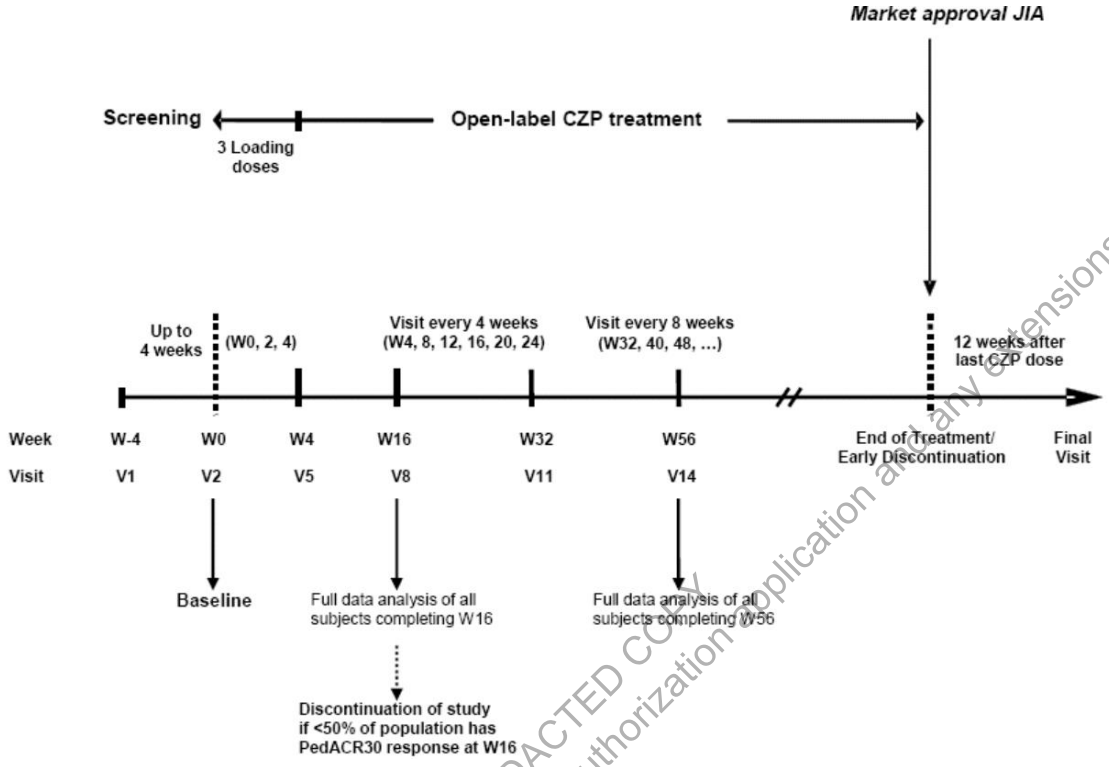
[u] CZP plasma level and anti-CZP antibodies to be measured at Weeks 4, 12, 16, and 24. A postdose CZP plasma sample will be collected at approximately 5 to 7 days following the Week 16 Visit (ie, requires an additional clinic site visit at Week 17).

Has been changed to:

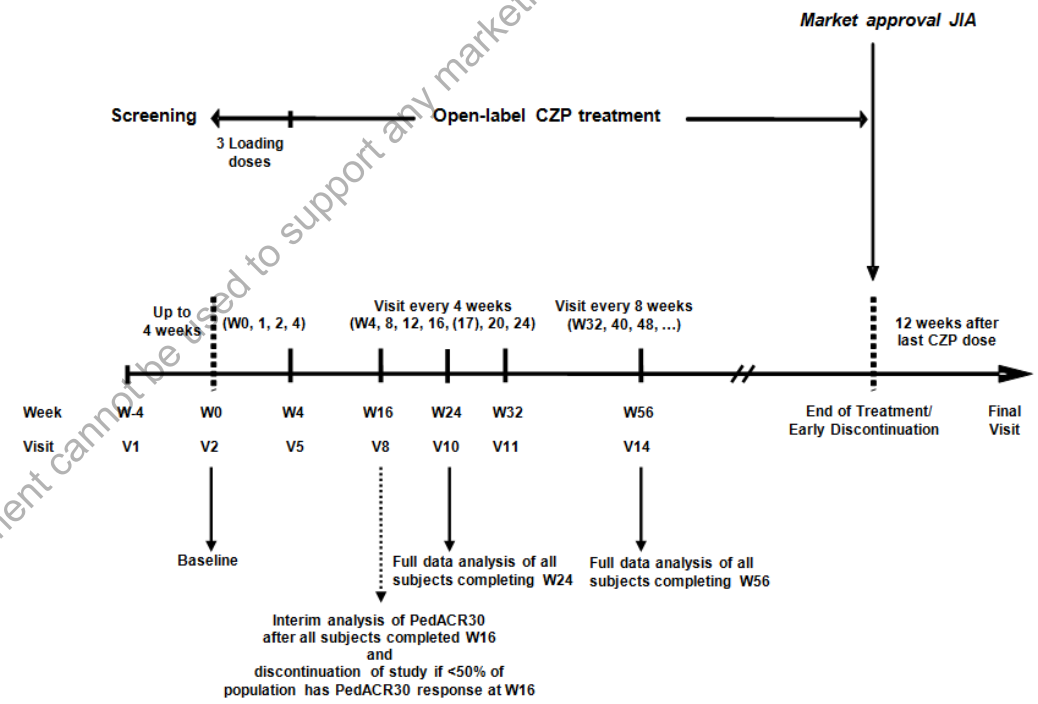
[u] CZP plasma level and anti-CZP antibodies to be measured at Weeks 4, 12, 16, and 24. A postdose CZP plasma sample will be collected at approximately 5 to 7 days following the Week 16 Visit (ie, requires an additional clinic site visit for blood collection at Week 17).

Change #33

Section 5.3 Schematic diagram:



Has been changed to:



Change #34

Section 5.4.2 Dose selection, the last sentence has been removed:

Interim data from the ongoing clinical study in children and adolescents with Crohn's disease (ages 6 to 17 years) confirm that the weight-based dose adjustment for pediatric study participants with Crohn's disease leads to similar plasma concentrations as observed previously in adult study participants with Crohn's disease.

Change #35

Section 6.1 Inclusion criteria, inclusion criterion 6:

6. Study participants must have had a diagnosis of JIA (according to the International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis, 2001) for at least 6 months prior to Baseline (Visit 2). Eligible JIA categories include: polyarthritis rheumatoid factor-positive, polyarthritis rheumatoid factor-negative, extended oligoarthritis, juvenile psoriatic arthritis, and ERA.

Has been changed to:

6. Study participants must have had onset of signs and symptoms consistent with a diagnosis of JIA (according to the International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis, 2001) and initiation of JIA treatment for at least 6 months prior to Baseline (Visit 2). Eligible JIA categories include: polyarthritis rheumatoid factor-positive, polyarthritis rheumatoid factor-negative, extended oligoarthritis, juvenile psoriatic arthritis, and ERA.

Change #36

Section 6.1 Inclusion criteria, inclusion criterion 8:

8. Study participants must have had an inadequate response to, or intolerance to, at least 1 DMARD (nonbiologic and biologic).

Has been changed to:

8. Study participants must have had an inadequate response to, or intolerance to, at least 1 DMARD (nonbiologic or biologic). For example, study participant had prior inadequate response to MTX (based on the Investigator's clinical judgment).

Change #37

Section 6.1 Inclusion criteria, inclusion criterion 9:

9. If the study participant is using MTX, then the dose must have been stable for at least 1 month before Screening at ≥10 to ≤15mg/m^2 per week. If the study participant is not using MTX, then the treatment must have been previously withdrawn for documented reasons of intolerability or inadequate response.

Has been changed to:

9. If the study participant is using MTX, then the study participant must have been on MTX for a minimum of 3 months at Screening. In addition, the dose must have been stable for at

least 1 month before Screening at ≥10 to ≤15mg/m^2 per week. If the study participant is not using MTX, then the treatment must have been previously withdrawn for documented reasons of intolerability or inadequate response.

Change #38

Section 6.2 Exclusion criteria, exclusion criterion 6, the exclusion criterion for biologic DMARDs infliximab and abatacept in Table 6-1 Prohibited medications at entry (Baseline):

Use of infliximab or abatacept within 84 days prior to the Baseline arthritis assessment.

Has been changed to:

Use of infliximab or abatacept within 60 days prior to the Baseline arthritis assessment.

Change #39

Section 6.2 Exclusion criteria, exclusion criterion 11:

11. Known TB disease, high risk of acquiring TB infection, or latent TB infection:

a. Known TB disease of either Study participant or Caregiver

- Currently active TB disease or clinical signs and symptoms suspicious for TB.
- Prior history of active TB disease involving any organ system (clinically documented).
- Chest radiograph evidence of past active TB disease (not clinically documented), which could include apical lung fibrosis, pleural thickening, calcified lung nodules, calcified hilar lymph nodes, pericardial calcification.

a. High risk of acquiring TB infection

- Known exposure of Study participant or Caregiver to another person with active TB disease ≤3 months prior to Screening.
- High risk of future exposure of Study participant or Caregiver to another person with active TB disease (eg, time spent in an institutional setting).

b. Latent TB infection - Study participants who don't meet criteria "a=known TB disease" or "b=high risk of acquiring TB infection" but do meet **any** of the following, **regardless of prior TB treatment**:

- Currently purified protein derivative (PPD) positive (+) (test must be performed ≤3 months prior to Screening).

  OR

- An alternative to the PPD skin test must be used if study participants meet the following criteria:
  - Study participants with documented history of severe positive PPD reaction, eg, necrosis, blistering, anaphylactic shock, or ulcerations (test performed >3 months prior to Screening), or

- Study participants with previous documented history of Bacille Calmette-Guérin (BCG) vaccination.

If any one of these 2 conditions is met, study participants must have a QuantiFERON® test conducted at Screening. If the result of the QuantiFERON is indeterminate, the test may be repeated once; if positive or indeterminate on retest, the study participant is excluded. The retest must be conducted in the allowable Screening window.

- Study participants with QuantiFERON (performed ≤3 months prior to Screening) positive or indeterminate are excluded.

- Exception from exclusion 11c is permitted only if treatment for latent TB infection is initiated or has been initiated at least 1 month prior to study medication administration and treatment is still ongoing at the time of study entry.
- A positive PPD is defined as ≥5mm of induration 48 to 72 hours after intradermal injection of 5TU of PPD-S or 2TU of PPD-RT23 regardless of the study participant's history of BCG vaccination.
- Reports of PPD results not taken at Screening but (performed ≤3 months prior to Baseline and) reported from elsewhere must be documented with exact induration measurement and date.
- Treatment for latent TB infection includes eg, isonicotinic acid hydrazide/isoniazid (INH) therapy for 9 months (with vitamin B6); another latent TB infection treatment regimen should be considered if the study participant is living in or has emigrated recently from a country with a high endemic rate of INH-resistant or multi-drug-resistant TB.

Has been changed to:

11. Study participants with known TB infection, at high risk of acquiring TB infection, or latent TB (LTB) infection are excluded:
    a. Known TB infection whether present or past is defined as:
        - Active TB infection or clinical signs and symptoms suspicious for TB (pulmonary or extra-pulmonary)
        - History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection
        - Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the study participant's medical history
    b. High risk of acquiring TB infection is defined as:
        - Known exposure of Study participant or Caregiver to another person with active TB infection within the 3 months prior to Screening

- Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection to Study participant or Caregiver is high

c. Latent TB infection (unless appropriate prophylaxis is initiated prior to study treatment according to Section 10.7.9.1.1 and continued to completion of prophylaxis) is defined as:

Absence of signs, symptoms (ie, evidence of organ-specific involvement), or physical findings suggestive of TB infection with a positive interferon-gamma release assay (IGRA [QuantiFERON]) test (or 2 indeterminate IGRA test results) or positive PPD (where the PPD skin test is approved for use by UCB; mandatory for ages 2 to 4 years in this study) or, if written documentation of Bacille Calmette-Guérin (BCG) vaccination is available for study participants ages 2 to 4 years, a TB questionnaire indicating an increased study participant's risk of exposure or infection with TB, and a chest x-ray (or other imaging) without evidence of TB infection.

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

Refer to Section 10.7.9 for additional information on TB definition and clinical signs, diagnosis, documentation, and treatment.

Study participants with a history of or active infection with nontuberculous mycobacteria (NTMB) are excluded from this study.

Change #40

Section 6.2 Exclusion criteria, exclusion criterion 12:

12. Study participant has a current sign or symptom which may indicate infection (eg, fever, cough), a history of chronic or recurrent infections (more than 3 episodes requiring antibiotics/antivirals during the 12 months prior to Screening [Visit 1]), had a recent (within the 6 months prior to Screening [Visit 1]) serious or life-threatening infection (including herpes zoster), or is at a high risk of infection in the Investigator's opinion (eg, study participants with leg ulcers, indwelling urinary catheter, and persistent or recurrent chest infections or permanently bed-ridden or wheelchair bound).

Has been changed to:

12. Study participant has a current sign or symptom which may indicate infection (eg, fever, cough), a history of chronic or recurrent infections within the same organ system (more than 3 episodes requiring antibiotics/antivirals during the 12 months prior to Screening [Visit 1]), had a recent (within the 6 months prior to Screening [Visit 1]) serious or life-threatening infection (including herpes zoster), or is at a high risk of infection in the Investigator's opinion (eg, study participants with leg ulcers, indwelling urinary catheter, and persistent or recurrent chest infections or permanently bed-ridden or wheelchair bound).

Change #41

Section 6.2 Exclusion criteria, exclusion criterion 13:

13. Study participant with known concurrent viral hepatitis or known positivity to hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody or known human immunodeficiency virus (HIV) infection.

Has been changed to:

13. Study participant with known concurrent viral hepatitis or known positivity for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody or known human immunodeficiency virus (HIV) infection. At Screening, a hepatitis panel result which indicates immunity due to hepatitis B vaccination is not considered an exclusion criterion.

Change #42

Section 6.2 Exclusion criteria, exclusion criterion 16:

16. Study participant is breast-feeding, pregnant or plans to become pregnant during the study or within 12 weeks following the last dose of study medication. Female study participants of childbearing potential (ie, postmenarcheal) must have a negative result at Screening and Baseline (Visits 1 and 2) pregnancy tests to be eligible for study entry.

Has been changed to:

16. Study participant is breast-feeding, pregnant or plans to become pregnant during the study or within 12 weeks following the last dose of study medication (or longer if required by local regulations). Female study participants of childbearing potential (ie, postmenarcheal) must have a negative result at Screening and Baseline (Visits 1 and 2) pregnancy tests to be eligible for study entry.

Change #43

Section 6.2 Exclusion criteria, exclusion criterion 17:

17. Study participant is a sexually active female of childbearing potential (ie, postmenarcheal) and is not practicing or will not agree to practice an effective means of birth control. For postmenarcheal female study participants not currently sexually active, the study participant and parent or legal representative should agree that the study participant will employ an effective means of birth control should the study participant become sexually active. Acceptable methods of birth control are: oral/parenteral/implantable hormonal contraceptives (stable at least 2 months prior to Screening (Visit 1) if initiated prior to entering the study) or a combination of barrier and spermicide. Study participants must agree to use adequate contraception during the study and for 12 weeks after their last dose of study medication. Male study participants who are sexually active must agree to ensure they or their female partner(s) uses adequate contraception during the study and for 12 weeks after the study participant receives their last dose of study medication. (Sexually active means engaging in sexual intercourse, regardless of frequency).

Has been changed to:

17. Study participant is a sexually active female of childbearing potential (ie, postmenarcheal) and is not practicing or will not agree to practice an effective means of birth control. For postmenarcheal female study participants not currently sexually active, the study participant and parent or legal representative should agree that the study participant will employ an effective means of birth control should the study participant become sexually active. Acceptable methods of birth control are: oral/parenteral/implantable hormonal contraceptives (stable at least 2 months prior to Screening (Visit 1) if initiated prior to entering the study) or a combination of barrier and spermicide. Study participants must agree to use adequate contraception during the study and for 12 weeks after their last dose of study medication (or longer if required by local regulations). Male study participants who are sexually active must agree to ensure they or their female partner(s) uses adequate contraception during the study and for 12 weeks after the study participant receives their last dose of study medication (or longer if required by local regulations). (Sexually active means engaging in sexual intercourse, regardless of frequency).

Change #44

Section 6.2 Exclusion criteria, exclusion criterion 24:

24. Study participant is wheelchair-bound.

Has been changed to:

24. Study participant is wheelchair-bound at the time of enrollment.

Change #45

Section 6.2 Exclusion criteria, a new exclusion criterion 25 has been added:

25. Study participant with a history of or active systemic/respiratory infection due to fungal, parasitic, or mycotic pathogens including but not limited to histoplasmosis, coccidiosis, paracoccidiosis, pneumocystis, blastomyces, and aspergillus.

    Radiographic evidence suggestive of any of these infections is sufficient grounds for exclusion.

Change #46

Section 6.3 Rescreening:

6.3 Rescreening

Rescreening is allowed after consultation with the Medical Monitor as per the following:

- Study participants with isolated exclusionary laboratory assessments at Screening may have this laboratory assessment repeated once if, in the Investigator's opinion, the value is not reflective of the study participant's previous clinical and laboratory pattern. Retesting must be completed within the stated Screening Period. If the repeat values are within the acceptable ranges of the study and the study participant remains eligible during the Baseline Visit (Week 0), the study participant may be dosed.

- Study participants who failed Screening (eg, due to transient out-of-range safety laboratory values or in the Investigator's judgment mild acute illness, eg, a cold) may be rescreened after complete recovery of the mild acute illness and/or normalization of the out-of-range safety laboratory values.

Has been changed to:

6.3 Retesting and rescreening

Retesting of laboratory assessments within the Screening Period is allowed as per the following:

- Study participants with isolated exclusionary laboratory assessments at Screening may have this laboratory assessment repeated once if, in the Investigator's opinion, the value is not reflective of the study participant's previous clinical and laboratory pattern. Retesting must be completed within the stated Screening Period. If the repeat values are within the acceptable ranges of the study and the study participant remains eligible during the Baseline Visit (Week 0), the study participant may be dosed.

Rescreening is only allowed after consultation with the Medical Monitor as per the following:

- Study participants who failed Screening (eg, due to transient out-of-range safety laboratory values or in the Investigator's judgment mild acute illness, eg, a cold) may be rescreened after complete recovery of the mild acute illness and/or normalization of the out-of-range safety laboratory values.
- Study participants with LTB infection, indicated by positive PPD skin test or positive IGRA test result (or TB questionnaire indicating an increased risk of exposure or infection with TB for study participants ages 2 to 4 years with documented BCG vaccination) and a chest imaging without evidence of TB infection at Screening, may be rescreened after initiation of treatment for latent TB. Prior to first study medication administration, TB treatment must have been ongoing for at least 4 weeks before enrollment will be allowed and after approval of the Medical Monitor. Treatment for TB must be continued until completion of 9 months of therapy (refer to Section 10.7.9).
- Rescreening might be allowed more than once but not in case of repeated occurrence of the same illness. All Screening assessments must be repeated as applicable in case of Rescreening. The maximum duration of the Rescreening Period is 28 days or 4 weeks. Rescreening must only be scheduled after an appropriate time period after the initial Screening Visit allowing for repetition of blood collection (depending on local requirements for maximum blood volumes; depending on study participant weight).
- All study participants who failed to be enrolled within the Screening Period of 28 days must be registered as Screen Failure in the interactive voice/web response system (IXRS). Study participants approved to be rescreened must be registered with a new study participant number.

Change #47

Section 6.4 Withdrawal criteria, the third withdrawal criterion:

3. Study participant develops confirmed latent or active TB once enrolled or discontinues treatment for latent TB prematurely or is noncompliant with anti-TB therapy in the Investigator's or Sponsor's opinion must discontinue further use of study medication and be immediately withdrawn from study participation (see Section 10.7.9).

Has been changed to:

3. Study participant who develops confirmed reactivation of latent or active TB or NTMB infection during the study (including, but not limited to, conversion demonstrated by IGRA or PPD or other diagnostic means, eg, TB questionnaire, during the course of the study) must be withdrawn.

Change #48

Section 6.4 Withdrawal criteria, a new withdrawal criterion has been added below withdrawal criterion 3, and subsequent criteria have been renumbered:

4. Study participant who prematurely discontinues treatment for LTB, or, in the opinion of the Investigator or Sponsor, is noncompliant with anti-TB therapy must be withdrawn.

Change #49

Section 7.2 Treatments to be administered, fourth paragraph, the last sentence:

In addition, study participants will have the option to either switch to home-based CZP injection or switch back to administration at the study site at anytime during the study.

Has been changed to:

In addition, if needed, home dosing can be performed by qualified health care professionals according to the written instructions for the correct sc injection technique provided by the site staff. Study participants will have the option to either switch to home-based CZP injection or switch back to administration at the study site at anytime during the study.

Change #50

Section 7.2 Treatments to be administered, the fifth paragraph:

The method of injection (ie, qualified site personnel-injection at study site; injection by the study participant/caregiver at the study site or at home) and the site of injection (abdomen, thigh) will be recorded in the CRF at each visit.

Has been changed to:

The method of injection (ie, qualified site personnel-injection at study site; injection by the study participant/caregiver or qualified health care professional at the study site or at home) and the site of injection (abdomen, thigh) will be recorded in the CRF at each visit.

Change #51

Section 7.4 Labeling, second paragraph, the third sentence:

The tear-off section will be removed and attached to the CRF at the time of study medication administration to the study participant and the main section will remain affixed to the individual container.

Has been changed to:

The tear-off section will be removed and attached to the source document at the time of study medication administration to the study participant and the main section will remain affixed to the individual container.

Change #52

Section 7.8.1 Permitted concomitant treatments (medications and therapies), the first bullet:

- MTX, if being used:
  - Must have been stable for at least 1 month before Screening (Visit 1) at ≥10 to ≤15mg/m^2 per week.
  - The maximum dose allowed during the study is 15mg/m^2 per week.
  - Prior to Week 16, route of administration must not change. After Week 16, the route of administration may be changed.
  - During the study, the MTX dose may be decreased, but not discontinued (except for documented reasons of intolerance or toxicity, or in association with study participants achieving CRM and after CZP was discontinued).
  - After discontinuation, MTX treatment can be restarted.

Has been changed to:

- MTX, if being used:
  - Must have been stable for at least 1 month before Screening (Visit 1) at ≥10 to ≤15mg/m^2 per week.
  - During the study, an increase is allowed only after Week 16 and to a maximum dose of 15mg/m^2 per week.
  - Prior to Week 16, route of administration must not change. After Week 16, the route of administration may be changed.
  - During the study, the MTX dose may be decreased, but not discontinued. Methotrexate may be discontinued only for documented reasons of intolerance or toxicity, or in study participants who achieve CRM and only after discontinuation of CZP.
  - Study participants who do not achieve persistent CRM status can reinitiate therapy with MTX.

Change #53

Section 7.8.1 Permitted concomitant treatments (medications and therapies), the fifth bullet:

- Corticosteroids:
  - At study entry, the dose should have been stable for at least 7 days prior to the Baseline joint examination at a maximum dose of 10mg or 0.2mg/kg prednisone (or equivalent) per day, whichever is the smaller dose.

- During the study, the dose of oral corticosteroids may be decreased but not initiated or increased above 10mg or 0.2mg/kg prednisone (or equivalent) per day, whichever is the smaller dose. The dose must be stable in the 7 days prior to a joint examination.
- Intra-articular (ia) corticosteroids may be administered no more frequently than every 4 months and no more than up to 3 times in 1 year and only into up to 3 joints at a single time point.
- If 1 or more joints have been injected (limited to 3 joints at a single time point), this/these joint(s) must be excluded from the PRINTO/PRCSG standard joint examination.
- Intravenous (iv) corticosteroid use is permitted only for stress dosing for the purposes of surgery.

Has been changed to:

- Corticosteroids:
  - At study entry, the dose should have been stable for at least 7 days prior to the Baseline joint examination at a maximum dose of 10mg or 0.2mg/kg prednisone (or equivalent) per day, whichever is the smaller dose.
  - During the study, the dose of oral corticosteroids may be decreased but not initiated or increased above 10mg or 0.2mg/kg prednisone (or equivalent) per day, whichever is the smaller dose. The dose must be stable in the 7 days prior to a joint examination.
  - Initiation of topical corticosteroids is allowed for treatment of uveitis if developed during the course of the study.
  - Intra-articular (ia) corticosteroids may be administered no more frequently than every 4 months and no more than up to 3 times in 1 year and only into up to 2 joints at a single time point.
  - Any joint injected with ia corticosteroids will be excluded from the efficacy analysis for a period of 3 months.
  - Intravenous (iv) corticosteroid use is permitted only for stress dosing for the purposes of surgery.

Change #54

Section 7.8.2 Rescue medication, the fourth and fifth paragraphs:

The following medications are defined as rescue medication in the first 16 weeks of this study:

- Initiation of MTX (if not being used at study entry), or increase of MTX above Baseline.
- Initiation of oral corticosteroids, or increase of oral corticosteroids above Baseline.
- Injection of intra-articular (ia) corticosteroids into more than 3 joints at a single time point.

- Injection of intra-articular (ia) corticosteroids into the same joint more frequently than 3 times in a 12-month period.
- Intravenous (iv) corticosteroids (any dose), if not used for stress dosing for the purposes of surgery.
- Intramuscular (im) corticosteroids.

The following medications are defined as rescue medication for the remainder of the study:

- Initiation of MTX (if not being used at study entry), and increase of MTX above 15mg/m^2 per week at any time.
- Initiation of oral corticosteroids, or increase to >10mg or 0.2mg/kg (whichever is the smaller dose).
- Injection of intra-articular (ia) corticosteroids into more than 3 joints at a single time point.
- Injection of intra-articular (ia) corticosteroids into the same joint more frequently than 3 times in a 12-month period.
- Intravenous (iv) corticosteroids (any dose), if not used for stress dosing for the purposes of surgery.
- Intramuscular corticosteroids (im).

Have been changed to:

The following medications are defined as rescue medication in the first 16 weeks of this study:

- Initiation of MTX (if not being used at study entry), or increase of MTX above Baseline.
- Initiation of oral corticosteroids, or increase above Baseline.

The following medications are defined as rescue medication after Week 16:

- Initiation of MTX (if not being used at study entry), and increase of MTX above 15mg/m^2 per week at any time.
- Initiation of oral corticosteroids, or increase to >10mg or 0.2mg/kg prednisone (or equivalent) per day, whichever is the smaller dose.

The following medications are defined as rescue medication when given at any time during the study:

- Injection of intra-articular (ia) corticosteroids into more than 2 joints at a single time point.
- Injection of intra-articular (ia) corticosteroids into the same joint more frequently than 3 times in a 12-month period.
- Intravenous (iv) corticosteroids (any dose), if not used for stress dosing for the purposes of surgery.

- Intramuscular (im) corticosteroids.

Change #55

Section 7.9 Enrollment and numbering of study participants, the second sentence:

The IVRS will provide the Investigator with the unique study participant number assigned to each study participant.

Has been changed to:

The Investigator will enter the unique study participant number assigned to each study participant, based on a predefined range of study participant numbers assigned to the Investigator's site.

Change #56

Section 8.1 Visit 1 (Week -4 to 0) Screening, the tenth bullet has been moved below the bullet "TB screening":

- TB questionnaire

Change #57

Section 8.1 Visit 1 (Week -4 to 0) Screening, a new bullet has been added above the 15th bullet "TB screening":

- Chest x-ray (only for study participants with positive IGRA or PPD testing)**

Change #58

Section 8.1 Visit 1 (Week -4 to 0) Screening, the 15th bullet:

- TB screening if not performed within 3 months of Screening: PPD skin test (or QuantiFERON required to be performed by the central lab if the study participant has a documented history of severe positive PPD reaction or a documented history of BCG vaccination)

Has been changed to:

- TB screening if not performed within 3 months of Screening: PPD skin test for study participants from 2 to 4 years of age (unless written documentation for BCG vaccination is available) or IGRA (to be performed by the central lab) for study participants from 5 to 17 years of age)**

Change #59

Section 8.1 Visit 1 (Week -4 to 0) Screening, the last bullet:

- IVRS phone call (to receive study participant number assignments)

Has been changed to:

- IXRS contact (to register study participant with unique study participant number)

Change #60

Section 8.1 Visit 1 (Week -4 to 0) Screening, the note at the end of the section:

*Change in height and weight over the last 6 months and over the last year will be collected via parent-/self-report, if available from medical records.

Has been changed to:

*Change in height and weight over the last 6 months and over the last year will be collected via parent-/self-report, if not available from medical records.

Change #61

Section 8.1 Visit 1 (Week -4 to 0) Screening, a new note has been added at the end of the section for chest x-ray, TB screening, and TB questionnaire:

**For details of TB screening and testing, see Section 10.7.9.

Change #62

Section 8.2 Visit 2 (Week 0) Baseline, the 19th and 20th bullets:

- FPS-R for study participants ages 5 to 11 years (at Baseline and daily assessment during the first 7 days of treatment)
- JIA Pain VAS for study participants ages 12 to 17 years; acute and standard versions (both at Baseline and daily assessment of the acute version during the first 7 days of treatment)

Has been changed to:

- FPS-R for study participants ages 5 to 11 years (at Baseline and daily assessment on Day 1 to Day 7)
- JIA Pain VAS for study participants ages 12 to 17 years; acute and standard versions (both at Baseline and daily assessment of the acute version on Day 1 to Day 7)

Change #63

Section 8.2 Visit 2 (Week 0) Baseline, the paragraph at the end of the section:

Documentation of the assessment of all 6 core set measures of PedACR response (PRINTO/PRCSG standard joint examination, Physician's Global Assessment of Disease Activity [VAS], CHAQ-parent reported, Parent's Assessment of Arthritis Pain [VAS], Parent's Global Assessment of Overall Well-Being [VAS] and DMS) **will be submitted to UCB or designee for immediate review of completeness, while the study participant is still on site.**

Has been changed to:

Documentation of the assessment of all 6 core set measures of PedACR response (PRINTO/PRCSG standard joint examination, Physician's Global Assessment of Disease Activity [VAS], CHAQ-parent reported, Parent's Assessment of Arthritis Pain [VAS], Parent's Global Assessment of Overall Well-Being [VAS] and CRP) **will be submitted to**

UCB or designee for immediate review of completeness, while the study participant is still on site.

Change #64

Section 8.3 Visits 3 and 4 (Weeks 1 and 2), the ninth bullet:

- Collection of JIA Pain VAS or FPS-R completed during the first 7 days of treatment

Has been changed to:

- Collection of JIA Pain VAS or FPS-R completed on Day 1 to Day 7

Change #65

Section 8.4 Visits 5 to 10 (Weeks 4, 8, 12, 16, 20, and 24), the paragraph at the end of the section:

Documentation of the **Week 16** assessment of all 6 core set measures of PedACR response (PRINTO/PRCSG standard joint examination, Physician's Global Assessment of Disease Activity [VAS], CHAQ-parent reported, Parent's Assessment of Arthritis Pain [VAS], Parent's Global Assessment of Overall Well-Being [VAS] and DMS) **will be submitted to UCB or designee for immediate review of completeness, while the study participant is still on site.**

Has been changed to:

Documentation of the **Week 16 and Week 24** assessment of all 6 core set measures of PedACR response (PRINTO/PRCSG standard joint examination, Physician's Global Assessment of Disease Activity [VAS], CHAQ-parent reported, Parent's Assessment of Arthritis Pain [VAS], Parent's Global Assessment of Overall Well-Being [VAS] and CRP) **will be submitted to UCB or designee for immediate review of completeness, while the study participant is still on site.**

Change #66

Section 8.5 Visits 11 and continuing (Week 32 and every 8 weeks thereafter), the eleventh bullet has been removed:

- TB screening is to be repeated every 48 weeks in those study participants with a negative TB test at their most recent assessment. A PPD skin test must be performed. (QuantiFERON required to be performed by the central lab if the study participant has a documented history of severe positive PPD reaction or a documented history of BCG vaccination) (Week 48 and every 48 weeks thereafter).

Change #67

Section 8.5 Visits 11 and continuing (Week 32 and every 8 weeks thereafter), the paragraph at the end of the section:

Documentation of the **Week 56** assessment of all 6 core set measures of PedACR response (PRINTO/PRCSG standard joint examination, Physician's Global Assessment of Disease Activity [VAS], CHAQ-parent reported, Parent's Assessment of Arthritis Pain [VAS], Parent's Global Assessment of Overall Well-Being [VAS] and DMS) **will be submitted to**

UCB or designee for immediate review of completeness, while the study participant is still on site.

Has been changed to:

Documentation of the **Week 56** assessment of all 6 core set measures of PedACR response (PRINTO/PRCSG standard joint examination, Physician's Global Assessment of Disease Activity [VAS], CHAQ-parent reported, Parent's Assessment of Arthritis Pain [VAS], Parent's Global Assessment of Overall Well-Being [VAS] and CRP) **will be submitted to UCB or designee for immediate review of completeness, while the study participant is still on site.**

Change #68

Section 9 Assessment of pharmacokinetics and immunological variables, the third, fourth, and fifth paragraphs:

Once at least 20 study participants (minimum 6 study participants in each age group: 2 to 5 years, 6 to 11 years, and 12 to 17 years) have completed Week 12 (Visit 7), PK data will be compared with plasma concentrations observed previously in adult study participants with RA.

This CZP plasma concentration analysis may be done in 2 or 3 stages if at least 20 study participants in total complete Week 12 (Visit 7) before 6 study participants in 1 or both of the other age groups have completed. The plasma concentration analysis would be performed on the available completed study participants in the first stage. The analysis would then be performed on the other age groups once the required minimum number of 6 study participants have completed Week 12 (Visit 7).

If plasma concentrations are not consistent with those observed in previous studies with adults, the dosing algorithm may be changed via a protocol amendment. This study will continue during the PK analysis. All study participants assessed in this analysis will continue treatment after Week 12 (Visit 7).

Have been changed to:

Plasma concentration data for CZP from this study will be compared with plasma concentrations observed previously in adult study participants with RA, as described in Section 13.7. This plasma concentration analysis will be done on an ongoing basis throughout the study, starting when 6 study participants in 1 of the age groups have completed Week 12 (Visit 7).

Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicate that no change to the dosing algorithm is required. If future analyses indicate that plasma concentrations are outside of the exposure range of those observed in previous studies with adults, the dosing algorithm may be changed via a protocol amendment, and if necessary additional interim analyses including PopPK, may be performed. This study will continue during the PK analysis. All study participants assessed in this analysis will continue treatment after Week 12 (Visit 7).

Change #69

Section 9 Assessment of pharmacokinetics and immunological variables, the following sentence has been added below the fourth paragraph:

The final pediatric PopPK model will be combined with PD data (PedACR) and if the data allow, an exposure-response relationship will be derived.

Change #70

Section 9 Assessment of pharmacokinetics and immunological variables, the following has been added at the end of the section:

These plasma samples may be used additionally for analyses of CZP and its constituent moieties using alternative assay methods. The results of the analyses of CZP and its constituent moieties from alternative methods may be reported separately.

Change #71

Section 10.1.8 Ongoing safety data review and oversight, second paragraph, the fourth and fifth sentences:

In addition, there will be a study-specific Safety Review Committee consisting of the UCB study physician, the UCB study GCSP representative, and an external pediatric rheumatologist experienced in the field and clinical studies in pediatrics and familiar with safety issues in this population. A charter will be developed to address the logistics of such a committee.

Has been changed to:

In addition, a Data and Safety Monitoring Board (DSMB) will periodically review all emerging safety data (see Section 13.7). The DSMB will function and meet on a regular basis as per the agreed upon charter.

Change #72

Section 10.1.8 Ongoing safety data review and oversight, the last sentence:

The Sponsor 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.

Has been changed to:

The Sponsor Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Drug Safety and Data Management representatives.

Change #73

Section 10.3 AEs of special interest:

10.3 AEs of special interest

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

- Adverse events of special interest must be reported immediately by the Investigator (see Section 10.4). The following are AEs of special interest for this study:
- Serious infections, including opportunistic infections
- Malignancies, including lymphoma
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leukopenia
- Serious bleeding events
- Lupus and lupus-like illness
- Serious skin reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrosis, and erythema multiforme)

The purpose of the AE of special interest list is to identify and capture product specific AEs/reactions requiring expedited reporting or close monitoring by 1 or more regulatory authorities or close monitoring required by UCB. This tool will help ensure that specific special reporting requirements from regulatory authorities and safety topics requiring close monitoring are appropriately identified, processed, reported, and monitored. The process also allows for detection of safety signals, signal evaluation, and the assessment of changes in the benefit-risk ratio of UCB products/compounds, based on all safety and benefit-risk information available for the protection of the patient.

Has been changed to:

10.3 AEs of interest

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

Adverse events of interest include:

- Serious infections, including opportunistic infections
- Malignancies, including lymphoma
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leukopenia
- Serious bleeding events

- Lupus and lupus-like syndrome
- Serious skin reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrosis, and erythema multiforme)

Adverse events of interest must be reported immediately by the Investigator (see Section 10.4).

The purpose of the AE of interest list is to identify and capture product specific AEs/reactions requiring expedited reporting or close monitoring by 1 or more regulatory authorities or close monitoring required by UCB. This tool will help ensure that specific special reporting requirements from regulatory authorities and safety topics requiring close monitoring are appropriately identified, processed, reported, and monitored. The process also allows for detection of safety signals, signal evaluation, and the assessment of changes in the benefit-risk ratio of UCB products/compounds, based on all safety and benefit-risk information available for the protection of the patient.

Change #74

Section 10.4 Immediate reporting of AEs, the third bullet:

- AE of special interest (see Section 10.3)

Has been changed to:

- AE of interest (see Section 10.3)

Change #75

Section 10.6 Laboratory measurements, the first and second paragraphs:

Hematology, biochemistry, urinalysis samples will be collected at Screening, Baseline, Weeks 4, 8, 12, 16, 20, 24, 32, every 8 weeks thereafter, the Early Discontinuation/End of Treatment Visit, and the Final Visit 12 weeks after the last dose of study medication. At Weeks 1 and 2, CRP samples will be collected only.

Retesting within the Screening Period is allowed after consultation with the Medical Monitor in case of reporting failure of laboratory results (eg, issues with transportation of samples).

Have been changed to:

Hematology, biochemistry, and urinalysis samples will be collected at Screening, Baseline, Weeks 4, 8, 12, 16, 20, 24, 32, every 8 weeks thereafter, the Early Discontinuation/End of Treatment Visit, and the Final Visit 12 weeks after the last dose of study medication. At Week 1, only CRP and PK samples will be collected and at Week 2, only CRP samples will be collected.

Retesting of laboratory assessments within the Screening Period is allowed in case of isolated exclusionary laboratory assessments at Screening if, in the Investigator's opinion, the value is not reflective of the study participant's previous clinical and laboratory pattern (see Section 6.3). In addition, retesting within the Screening Period is allowed in case of reporting failure of laboratory results (eg, issues with transportation of samples).

Change #76

Section 10.6 Laboratory measurements, the following sentence has been added at the end of the sixth paragraph:

Only samples for CRP, PK, and immunological variables will then be collected at Baseline (Week 0).

Change #77

Section 10.6 Laboratory measurements, seventh paragraph, the second sentence:

The planned total blood volumes collected at a single time point (visit) will not exceed approximately 8mL.

Has been changed to:

The planned total blood volumes collected at a single time point (visit) will vary between 2mL and 9mL.

Change #78

Section 10.6 Laboratory measurements, the eighth to tenth paragraphs:

In addition, treatment of the veinpuncture site with an anesthetic cream prior to dosing is permitted.

If QuantiFERON testing is required to be performed by the central lab (for study participants with documented history of severe positive PPD reaction or previous documented history of BCG vaccination, see Section 6.2) additional blood sampling of approximately 3ml will be required at Screening.

If the result of the QuantiFERON is indeterminate, the test may be repeated once. The retest must be conducted in the allowable Screening window. Study participants with QuantiFERON (performed ≤3 months prior to Screening) positive or indeterminate are excluded.

Have been changed to:

In addition, treatment of the venipuncture site with an anesthetic cream prior to blood sampling is permitted.

If IGRA testing is required to be performed by the central lab (for all study participants from 5 to 17 years of age, see Section 6.2) additional blood sampling of approximately 3mL will be required at Screening.

If the result of the IGRA is indeterminate, the test may be repeated once. The retest must be conducted in the allowable Screening window. Study participants with IGRA (performed ≤3 months prior to Screening) positive or indeterminate and a chest x-ray confirmative of TB infection are excluded (see Section 10.7.9.2).

For study participants from 2 to 4 years of age, PPD testing will be performed locally (except for study participants with documented BCG vaccination) as described in Section 10.7.9.2.3.

Change #79

Section 10.6 Laboratory measurements, the sentence above the table and Table 10-2 Laboratory measurements:

The central laboratory will analyze and assess blood and urine samples for the following (except urine pregnancy test):

Table 10-2 Laboratory measurements

Hematology	Serum biochemistry	Urinalysis
Red blood cells	Sodium	pH
Hemoglobin	Potassium	Protein
Hematocrit	Chloride	Glucose
Platelets	Bicarbonate	Blood
White blood cells	Total calcium	Microscopy (WBC, RBC, casts, crystals, bacteria) (Microscopy will be performed only when there are abnormalities on dipstick)
Neutrophils	Inorganic phosphorus	
Lymphocytes	Creatinine kinase	
Monocytes	Glucose	
Eosinophils	Creatinine	
Basophils	Uric acid	**Serum pregnancy test[a]**
	Urea	
	Total protein	
	Albumin	**Hepatitis screening[b]**
	Alkaline phosphatase	HBcAb
	Gamma glutamyl tranferase	HBsAb
	Aspartate aminotransferase	HBsAg
	Alanine aminotransferase	HCVAb
	Bilirubin	HBV DNA, if applicable
	Total cholesterol	
	CRP	**TB screening[c]**
	Autoantibodies (ANA and anti-dsDNA antibodies)	QuantiFERON

ANA=antinuclear antibody; anti-dsDNA antibodies=double-stranded deoxyribonucleic acid antibody; CRP=C-reactive protein; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; RBC=red blood cells; WBC=white blood cells

[a] Serum pregnancy tests will be performed at Screening by the central laboratory (see Section 10.7.7). At Baseline, Weeks 8, 16, 24, and every visit thereafter, urine pregnancy tests will be performed locally.

[b] Study participants will be tested for hepatitis at Screening. HBV DNA is required for study participants with only positive HBcAb (negative HBsAg and HBsAb) or only positive HBsAg

[c] Only study participants with documented history of severe positive PPD reaction or previous documented history of BCG vaccination, see Section 6.2.

Note: Other pharmacokinetic assessments may be periodically performed as per Section 9.

Have been changed to:

The central laboratory will analyze and assess blood and urine samples for the following (except dip stick test and urine pregnancy test); other PK assessments may be periodically performed as per Section 9:

Table 10-2 Laboratory measurements

Hematology	Serum biochemistry	Urinalysis
Red blood cells	Sodium	pH[a]
Hemoglobin	Potassium	Protein[a]
Hematocrit	Chloride	Glucose[a]
Platelets	Bicarbonate	Blood[a]
White blood cells	Total calcium	Microscopy (WBC, RBC, casts, crystals, bacteria) (Microscopy will be performed only when there are abnormalities on dipstick)[a]
Neutrophils	Inorganic phosphorus	
Lymphocytes	Creatinine kinase	
Monocytes	Glucose	
Eosinophils	Creatinine	
Basophils	Uric acid	**Serum and urine pregnancy test[b]**
	Urea	
	Total protein	
	Albumin	**Hepatitis screening[c]**
	Alkaline phosphatase	HBcAb
	Gamma glutamyl transferase	HBsAb
	Aspartate aminotransferase	HBsAg
	Alanine aminotransferase	HCVAb
	Lactate dehydrogenase	HBV DNA, if applicable
	Bilirubin	
	Total cholesterol	**TB screening[d]**
	CRP	IGRA (ages 5-17 years),
	Autoantibodies (ANA and anti-dsDNA antibodies)	PPD (ages 2-4 years)

ANA=antinuclear antibody; anti-dsDNA antibodies=double-stranded deoxyribonucleic acid antibody; BCG=Bacille Calmette-Guérin; CRP=C-reactive protein; DNA=deoxyribonucleic acid; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; IGRA=interferon-gamma release assay; RBC=red blood cells; TB=tuberculosis; WBC=white blood cells
Note: The Screening Visit must be completed at least 4 to 12 working days prior to the Baseline Visit, depending on regional requirements and laboratory assessments required for the study participant (refer to laboratory manual for country-specific requirements). In case HBV DNA or TB IGRA is to be analyzed, the Baseline Visit can be performed at the earliest 12 days after the Screening Visit (6 working days in Russia). Study participants can only be enrolled into the study after all laboratory results of the Screening Visit have been confirmed.

[a] Urine dipsticks will be done locally at the site; only abnormalities will be reported. In case of abnormalities on dipstick, microscopy will be performed by the central laboratory.

[b] Serum pregnancy tests will be performed at Screening by the central laboratory (see Section 10.7.7). At Baseline, Weeks 8, 16, 24, and every visit thereafter, urine pregnancy tests will be performed locally.

[c] Study participants will be tested for hepatitis at Screening. HBV DNA is required for study participants with only positive HBcAb (negative HBsAg and HBsAb) or only positive HBsAg. A hepatitis panel result which indicates immunity due to hepatitis B vaccination is not considered an exclusion criterion.

[d] IGRA testing is required at Screening for all study participants aged 5 to 17 years; PPD testing is required for all study participants aged 2 to 4 years (except for study participants with documented BCG vaccination).

Change #80

Section 10.7.1 Vital signs, the first sentence:

Vital signs will be measured within approximately 15 minutes prior to dosing with study medication.

Has been changed to:

Vital signs will be measured within approximately 15 minutes prior to dosing and in addition (pulse and blood pressure only) approximately 30 minutes after dosing with study medication.

Change #81

Section 10.7.9 Assessment and management of TB and TB risk factors:

10.7.9.1 Assessment and management of TB and TB risk factors

As TNF-antagonists are known to be associated with significant risk of reactivation of latent TB, appropriate rigorous precautions are being taken within the protocol to address this. For inclusion in the study, see Section 6.2 (Exclusion Criterion 11).

Study participants who develop evidence of latent or active TB during the study must immediately discontinue further administration of study medication. Once withdrawn from study treatment, study participants should return for the Early Discontinuation Visit, complete all Early Discontinuation assessments, and complete a Final Visit 12 weeks after the last dose of study medication.

10.7.9.1 Tuberculosis assessments

10.7.9.1.1 Tuberculin purified protein derivative (PPD) skin test

A Mantoux tuberculin skin test must be performed preferably at the Screening Visit but at least within 3 months prior to Screening following the instructions below. Multiple puncture tests like the Tine and Heaf tests are not acceptable methods of testing because the amount of tuberculin injected intradermally cannot be precisely controlled.

If the skin test is positive, induration will be seen at and around the place of injection or puncture. The size (diameter) of the induration is measured and recorded. The results of the test are assessed in accordance to the criteria set in Section 6.2 (Exclusion Criterion 11).

10.7.9.1.2 Administration of the Mantoux tuberculin skin test

The intradermal injection of a measured amount of tuberculin is the standard method of detecting infection with *Mycobacterium tuberculosis*. One-tenth milliliter of PPD (ie, 5TU PPD-S or 2TU of PPD-RT 23, as recommended by the World Health Organization) is injected into the inner surface of the forearm. Other areas may be used, but the forearm is preferred. The use of a skin area free of lesions and away from veins is recommended. The injection is made using a one-quarter- to one-half-inch (1cm), 27G needle and a tuberculin syringe. The tuberculin should be injected by a qualified health care worker just beneath the surface of the skin, with the needle bevel upward. A discrete, pale elevation of the skin (a wheal) 6 to 10mm in diameter should be produced when the injection is done correctly. If it is

recognized that the first test was improperly administered, another test dose can be given at once, selecting a site several centimeters away from the original injection. A note in the record should indicate the site chosen for the second test. The study study participant should be instructed not to scratch the site and to avoid covering the area with a bandage.

Tests should be read by a trained health care worker between 48 and 72 hours after injection. If a study participant fails to return within 72 hours and has a negative skin test, tuberculin testing should be repeated. If a positive PPD is read after 72 hours, the study participant will be considered to be TB positive. Study participants should never be allowed to read their own tuberculin skin tests.

The reading should be performed in good light, with the forearm slightly flexed at the elbow. The basis of reading is the presence or absence of induration. Erythema should not be measured. The presence or absence of induration may be determined by inspection (from a side view against the light as well as by direct light) and by palpation. The diameter of induration should be measured transversely to the long axis of the forearm and recorded in millimeters, even for those tests classified as negative (ie, 0mm).

An induration of 5mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB. In most countries, the most conservative definition of positivity, ie, an induration of 5mm or greater, in response to the tuberculin skin test is reserved for immunocompromised study participants. This definition is to be applied here to maximize the likelihood of detecting latent TB.

T-cell interferon gamma release assays

A QuantiFERON®-TB GOLD must be done at the Screening Visit in those study participants with a documented history of severe positive PPD reaction or a documented history of BCG vaccination. Mantoux tuberculin skin testing must be done on all other study participants.

10.7.9.1.3 Tuberculosis questionnaire

The questionnaire “Evaluation of signs and symptoms of tuberculosis” (see Appendix 17.9) should be used as a source document. The questionnaire will be completed at Screening, Baseline, Weeks 12 and 24, every 16 weeks thereafter, and at the Early Discontinuation/End of Treatment Visit. The questionnaire will be completed by the Investigator or designee twice at each visit, once for the study participant and once for the caregiver and appropriately identified (ie, labeled study participant or caregiver). The questionnaire will assist with the identification of study participants who may require therapy for TB. A study participant/caregiver who answers “Yes” to the question “Has the study participant/caregiver been in close contact with an individual with active TB, or an individual who has recently been treated for TB?” at Screening is excluded. A “Yes” response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if study participant has latent or active TB (see Exclusion Criterion 11, Section 6.2). A “Yes” response to any of the questions during the study should trigger further careful assessment to determine if the study participant has TB (regardless if latent or active) and has to be withdrawn from the study.

Responses to the questions and the Investigator’s assessment of the study participant’s status and any action taken must be recorded in the source documents.

10.7.9.2 Tuberculosis management

For inclusion in the study, see Section 6.2 (Exclusion Criterion 11).

It is the Sponsor's requirement that all study participants who are on latent TB treatment at Baseline must comply with the full therapy course (see Section 6.2, Exclusion Criterion 11). Study participants who discontinue treatment for latent TB prematurely or who are noncompliant with anti-TB therapy in the Investigator's or Sponsor's opinion must discontinue further use of study medication and be immediately withdrawn from study participation. Once withdrawn from study treatment, study participants should return for the Early Discontinuation Visit to complete all early withdrawal assessments, and complete the Final Visit 12 weeks after the last dose of study medication.

Study participants that develop evidence of latent or active TB once enrolled in the study and receiving IMP must immediately discontinue further administration of study medication until diagnosis is confirmed. If latent or active TB is confirmed, the study participant also must be withdrawn immediately from the study. The study participant must return for the Early Discontinuation Visit to complete all early withdrawal assessments, and complete the Final Visit 12 weeks after the last dose of study medication. Confirmed active TB (ie, positive culture or acid-fast bacilli smear) is an SAE which must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirement until such time as the TB infection resolves. Confirmed latent TB should be recorded both as an AE and the reason for discontinuation from the study.

Follow-up information of suspected and confirmed TB cases should be provided to UCB at least after 3, 9, and 12 months of start date of anti-TB treatment, including hematological and biochemical safety parameters, x-ray evolution data, and TB diagnostic procedures used to follow-up and confirm recovery of TB.

Has been changed to:

10.7.9 Tuberculosis guidance, testing, and screening

10.7.9.1 Guidance

TNFα-inhibitors are known to be associated with an increased risk of TB and therefore, precautions are taken within the protocol to mitigate this risk. Study participants who develop signs or symptoms that may indicate latent TB infection or active TB during the Treatment Period must immediately discontinue further administration of IMP. Additional actions required are provided below. The Investigator should consider all potential sites of infection when assessing for TB during the study participant's history and the physical examination, and other evaluations. Sites commonly infected by TB include: the lungs, larynx, lymph glands, pleura, gastrointestinal system, genito-urinary tract (including renal), bones and joints, meninges, peritoneum, pericardium, and skin. This is not an exhaustive list and unusual presentations and areas of involvement should always be considered. Common symptoms that the study participant may present with include cough, blood in sputum, night sweats, lymphadenitis, joint pain/swelling, spinal deformity, headache/confusion, abdominal pain mimicking inflammatory bowel disease (IBD), frequent or painful urination, scrotal mass in men and pelvic inflammatory disease in women as well as other symptoms, or

nonspecific symptoms. This is not an exhaustive list and unusual presentations should always be considered.

Note that study participants with a history of NTMB or active NTMB infection are excluded from the study regardless of prior or current therapy.

10.7.9.1.1 Latent tuberculosis infection

Per exclusion criterion 11c, LTB infection is defined as a positive TB test (IGRA or PPD) and chest imaging without positive findings for TB along with the absence of signs, symptoms, or physical findings suggestive of TB infection. If available, smears and cultures of secretions or tissues should also be negative. At Screening, study participants who have recently (defined as no more than 12 months prior to Screening) completed a full course of prophylaxis for LTB infection may be considered for study participation. Study participants who have received prophylactic therapy for LTB infection for at least 4 weeks prior to enrollment (initiation of CZP treatment at Baseline) and are committed to completing the full course of therapy, may be considered for study participation. The Investigator must provide documentation of duration, and start and stop date of such therapy and method of therapy (eg, self-administration or directly observed therapy). This evidence of treatment should be recorded contemporaneously with the treatment date and should be filed in the source document. The Investigator must assess that the study participant's likelihood of completing the therapy is high and duly record their opinion in the study participant's record prior to enrolling the study participant. The Investigator must discuss each case with the Study Physician or Medical Monitor prior to allowing the study participant to be screened (in event the LTB infection was discovered prior to study participant screening) or enrolled (if LTB infection was identified at Screening).

Study participants with LTB infection, indicated by positive PPD skin test or positive IGRA test result (or TB questionnaire indicating an increased study participant's risk of exposure or infection with TB for study participants ages 2 to 4 years with documented BCG vaccination) and a chest imaging without evidence of TB infection at Screening, may be rescreened after initiation of treatment for latent TB and after approval of the Medical Monitor. Prior to first study medication administration TB treatment must have been ongoing for at least 4 weeks before enrollment will be allowed. Treatment for TB must be continued until completion of 9 months of therapy.

Prophylaxis may include isonicotinic acid hydrazide/isoniazid [INH] therapy (with vitamin B_6) for 9 months or any other locally approved therapy or combination regimen/therapy appropriate for immunosuppressed study participants. For study participants living in or recently emigrated (within 5 years prior to initiation of Screening) from a country or region with a high endemic rate of INH resistant or multidrug resistant TB, an approved combination therapy must be followed that is both approved for the region in which the infection was likely to have originated and targeted to the study participant's specific TB infection. If there is disagreement between the local guidelines and the UCB standards, the more stringent guidance will apply and should be considered appropriate for the study participant's specific TB infection.

Study participants with LTB infection must not undergo repeat PPD testing. The IGRA test should be used for any protocol-mandated TB screening, except for study participants who are 2 to 4 years of age and for whom the PPD test is the mandatory test in this study, unless written documentation of a BCG vaccination is available.

LTB infection and active TB identified during study

During the study, study participants who develop evidence of LTB infection or active TB must immediately discontinue further administration of IMP, be scheduled for the Early Discontinuation Visit and Final Visit, and referred to a TB specialist for evaluation. Evidence of LTB infection is defined as study participant's IGRA test converts to positive or indeterminate (and confirmed indeterminate on repeat), or PPD converts to positive (this only applies for regions or sites where UCB has determined PPD may be used for screening and follow-up), or the study participant's questionnaire or history and physical examination indicates that TB infection or exposure may have occurred. Evidence of active TB includes, in addition to the aforementioned tests, signs and symptoms of organ involvement. In either situation, the study participant should be carefully assessed by a TB specialist for active TB (see Section 10.7.9.1). Study participants diagnosed with active TB or LTB infection should receive appropriate TB or prophylaxis therapy respectively per local and UCB guidelines as described above. Any presumptive diagnosis or diagnosis of LTB infection or active TB is a reportable event; refer to Section 10.2.2 for details. The Investigator is to complete and submit the TB follow-up form provided.

The study participant should be transferred to the care of their physician and managed according to the best available standard of care. Study participants identified as having converted to LTB infection or active TB during the study must be scheduled to return for the Early Discontinuation Visit as soon as possible but no later than the next scheduled study visit. The study participant should be encouraged to keep the Final Visit as specified by the protocol.

If infection with NTMB is identified during the study, the same procedure as for active TB acquired during the study must be followed.

10.7.9.2 TB screening and testing

10.7.9.2.1 Chest x-ray

A chest radiograph (anterior-posterior view at minimum, but preferably anterior-posterior and lateral) must be taken for study participants with a positive or repeatedly indeterminate IGRA or PPD testing or TB questionnaire indicating an increased study participant's risk of exposure or infection with TB (study participants 2 to 4 years of age with a written documentation of BCG vaccination) at Screening. If a study participant has had a recent radiograph of the chest within approximately 3 months prior to Screening, it may be used in lieu of the protocol-required radiograph. All chest imaging must be read by a qualified radiologist/pulmonary physician who is specifically required to look for evidence of active TB or inactive TB.

Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified

granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

The chest x-ray (or, if done, Computed Axial Tomography of the Chest) must be negative for TB infection as determined by a qualified radiologist/pulmonary physician. All chest imaging (particularly x-rays) should be available for review by the Investigator before enrollment of the study participant.

10.7.9.2.2 Interferon-gamma release assay (IGRA test)

The IGRA (QuantiFERON®-TB GOLD In-Tube test) is the protocol-required method of screening for TB in study participants from 5 to 17 years of age and will be performed at the central laboratory. The IGRA and PPD skin test may not be performed at the same time and a positive or indeterminate outcome in 1 test may not be overruled by a negative result in the other. If the result of the IGRA test is indeterminate, the test may be repeated once. If positive or indeterminate on retest, the study participant may not be enrolled without further evaluation and treatment, as well as discussion by the Investigator with the Study Physician or Medical Monitor. The retest must be done during the protocol-defined Screening window.

10.7.9.2.3 Tuberculin Purified Protein Derivative (PPD skin test)

In study participants from 2 to 4 years of age (except for study participants 2 to 4 years of age with a written documentation of BCG vaccination), the PPD skin test must be administered during Screening or within the 3 months prior to Screening in accordance with the instructions below.

PPD skin test administration guidance:

The PPD skin test should be administered by a qualified health care professional. The injection is made intradermally into the inner surface of the forearm using a 27-gauge needle and tuberculin syringe using one-tenth milliliter of PPD (5TU PPD-S or 2TU of PPD-RT 23). If necessary, a site on the anterior thigh may be used. The site on the forearm used for administration should be free of lesions and away from superficial veins. A discrete, pale elevation of the skin (a wheal) 6 to 10mm in diameter should be produced when the injection is done correctly. If it is recognized that the first attempt was improperly administered, another attempt may be made using a new site that is at least 3cm away from the original. The site used for the second test should be recorded in the source documents. The study participant should be instructed to refrain from scratching the site and to avoid covering the area with a bandage.

The PPD skin test must be interpreted by a trained health care professional between 48 and 72 hours after administration. The reading should be done in a good light, with the forearm slightly flexed at the elbow. The presence or absence of induration, as determined by inspection and by palpation is the basis for interpreting the result. The diameter of induration is measured transversely to the long axis of the forearm and recorded in millimeters. Erythema should not be measured. An induration greater than or equal to 5mm is considered positive for the purposes of this study; regardless of study participant's history of vaccination with BCG. Study participants are not permitted to read their own PPD skin tests. If a study participant fails to return within 72 hours and has a negative skin test, the PPD skin test must

be repeated. Documentation must include a record of the date, time, and site of the test, and the date and time the test was read with exact induration measurement.

The PPD skin test should not be applied to study participants with the following history:

- History of severe positive PPD reaction, or
- History of a positive PPD skin test
- History of BCG vaccination regardless of time since vaccination
- History of positive IGRA test (or 2 indeterminate IGRA tests)

10.7.9.3 TB questionnaire (evaluation of signs and symptoms associated with TB and guidelines for evaluating exposure risk)

A questionnaire "Evaluation of Signs and Symptoms of Tuberculosis" will be provided as a source document (see Appendix 17.9). The questionnaire will assist study sites with the identification of study participants that may require prophylactic therapy for TB as well as suspect new cases of active TB. In this study, the TB questionnaire will be completed for study participant and parent/caregiver at the following visits: Screening, Baseline, Weeks 12 and 24, every 16 weeks thereafter, and at the Early Discontinuation/End of Treatment Visit.

Responses of "yes" to any of the items on the questionnaire may indicate that a study participant's risk of exposure or infection with TB has increased. This should prompt the Investigator to further examine the circumstances and consider initiating investigations necessary to rule out infection with TB. Depending on the outcome of the investigations, the Investigator will determine if prophylaxis or treatment for TB is required. Any presumptive diagnosis or diagnosis of LTB infection or active TB is a reportable event; refer to Section 10.2.2 for details. The Investigator is to complete and submit the TB follow-up form provided.

Change #82

Section 11.1 PedACR30, PedACR50, PedACR70, and PedACR90 clinical response, the fourth bullet:

- CHAQ completed by parent or caregiver (including the Parent's Assessment of Arthritis Pain [VAS]) (Appendices 17.1 and 17.2)

Has been changed to:

- CHAQ completed by parent or caregiver (Appendix 17.1)

Change #83

Section 11.1 PedACR30, PedACR50, PedACR70, and PedACR90 clinical response, the bolded sentence at the end of the section:

Documentation of the assessment of all 6 core set measures will be submitted to UCB or designee for immediate review of completeness at Week 0 (Baseline), Week 16, and Week 56, while the study participant is still on site.

Has been changed to:

Documentation of the assessment of all 6 core set measures will be submitted to UCB or designee for immediate review of completeness at Week 0 (Baseline), Week 16, Week 24, and Week 56, while the study participant is still on site.

Change #84

Section 11.2 PRINTO/PRCSG standard joint examination, second paragraph, the second sentence:

The assessment for swelling is made on 67 joints from the above list.

Has been changed to:

The assessment for swelling is made on 66 joints from the above list.

Change #85

Section 11.5 Childhood Health Assessment Questionnaire (CHAQ), third paragraph, the third sentence:

The same parent/caregiver should complete the questionnaires for each visit.

Has been changed to:

Preferably, the same parent/caregiver should complete the questionnaires for each visit. The questionnaire will not be collected if the study participant is not living with a parent/caregiver at least part-time, ie, if the parent/caregiver is not able to answer the questions appropriately.

Change #86

Section 11.6 Parent's Assessment of Arthritis Pain (VAS), second paragraph, the third sentence:

The same parent/caregiver should complete the scale for each visit.

Has been changed to:

Preferably, the same parent/caregiver should complete the scale for each visit. The scale will not be completed if the study participant is not living with a parent/caregiver at least part-time, ie, if the parent/caregiver is not able to answer the question appropriately.

Change #87

Section 11.7 Parent's Global Assessment of Overall Well-Being (VAS), second paragraph, the third sentence:

The same parent/caregiver should complete the scale for each visit.

Has been changed to:

Preferably, the same parent/caregiver should complete the scale for each visit. The scale will not be completed if the study participant is not living with a parent/caregiver at least part-time, ie, if the parent/caregiver is not able to answer the question appropriately.

Change #88

Section 11.9 Juvenile Arthritis Disease Activity Score 75-joint (JADAS-75), the heading and the first paragraph:

11.9 Juvenile Arthritis Disease Activity Score 75-joint (JADAS-75)

The change in the JADAS-75 from Baseline will be assessed. The JADAS-75 is a composite disease activity score based on a 75-joint count and includes the measures (normalized as needed): Physician's Global Assessment of Disease Activity (VAS) (0 to 10), the Parent's Global Assessment of Overall Well-Being (VAS) (0 to 10), the active joint count (0 to 75), and CRP (0 to 10) (Consolaro et al, 2009; Nordal et al, 2010).

Have been changed to:

11.9 JADAS

The change in the JADAS from Baseline will be assessed. The JADAS-71 is a composite disease activity score based on a 71-joint count and includes the measures (normalized as needed): Physician's Global Assessment of Disease Activity (VAS) (0 to 10), the Parent's Global Assessment of Overall Well-Being (VAS) (0 to 10), the active joint count (0 to 71), and CRP (0 to 10) (Consolaro et al, 2009; Nordal et al, 2010).

Change #89

Section 11.10 Clinically Inactive Disease and clinical remission, first paragraph, the fifth bullet:

- Physician's Global Assessment of Disease Activity score of ≤5mm on a 100mm VAS

Has been changed to:

- Physician's Global Assessment of Disease Activity score of best possible on the scale used (0mm on the 100mm VAS)

Change #90

Section 11.11 Duration of morning stiffness (DMS), the second sentence:

The study participant/caregiver will be asked the following question (Kirwan, JR and Reeback TS, 1986):

Has been changed to:

The study participant/caregiver will be asked the following question (Kirwan and Reeback, 1986):

Change #91

Section 11.12 Faces Pain Scale-Revised (FPS-R), the following has been added at the end of the first paragraph:

Study participants enrolled at 5 to 11 years of age will continue with the FPS-R when reaching 12 years of age. Completion of the FPS-R will not be required for study participants enrolled at 2 to 4 years of age if they reach 5 years of age during the study.

Change #92

Section 11.13 Patient's Assessment of Arthritis Pain (JIA Pain VAS), the first sentence:

In the JIA Pain VAS, study participants ages 12 to 17 years are asked the following question "How much pain have you had because of your illness today (acute version)/in the past week (standard version)?" (as applicable).

Has been changed to:

In the JIA Pain VAS, study participants aged 12 years or older are asked the following question "How much pain have you had because of your illness today (acute version)/in the past week (standard version)?" (as applicable).

Change #93

Section 11.14 Fatigue Assessment Scale (NRS), fourth paragraph, the third and fourth sentences:

The same parent/caregiver should complete the questionnaires for each visit. The questionnaire should be checked by site personnel for completeness.

Have been changed to:

Preferably, the same parent/caregiver should complete the scale for each visit. The scale will not be completed if the study participant is not living with a parent/caregiver at least part-time, ie, the parent/caregiver is not able to answer the question appropriately. The scale should be checked by site personnel for completeness.

Change #94

Section 11.15 Juvenile Arthritis School Attendance and Caregiver Work Productivity Survey, the following sentence has been added at the end of the first paragraph:

For further information please see the instructions provided on the worksheet.

Change #95

Section 12.2.1 Definition of source data, fourth paragraph, the first sentence:

Source documents that are computer-generated and stored electronically must be printed for review by the monitor (eg, ECG reports).

Has been changed to:

Source documents that are computer-generated and stored electronically do not need to be printed if the electronic medical record system at the investigational site is 21CFR Part 11 compliant. If the system is not 21CFR Part 11 compliant, the source data must be printed for review by the monitor (eg, ECG reports).

Change #96

Section 12.2.2 Source data verification, the following has been added below the first paragraph:

The procedures for conducting SDV on computerized study participant records (if the system is 21CFR Part 11 compliant) are the same as those for paper records. Source data verification is performed by reviewing the electronic record directly.

Change #97

Section 12.4 Termination of the study, the first sentence:

If, in the results of the first interim analysis, less than 50% of the study population achieves at least a PedACR30 response at Week 16, the study will be discontinued.

Has been changed to:

If, in the results of the first interim analysis, less than 50% of the study population achieves a PedACR30 response at Week 16, the study will be discontinued.

Change #98

Section 13.1 Definition of analysis sets, the following set has been removed:

- The Per-Protocol Set (PPS) will consist of study participants in the FAS who have completed a prespecified minimal exposure to the treatment regimen without any important protocol deviations that may influence the validity of the efficacy data.

Change #99

Section 13.1 Definition of analysis sets, the following set has been added:

- The Pharmacokinetic-Pharmacodynamic (PK-PD) Population will consist of all study participants in the SS who have at least 1 post-Baseline plasma concentration measurement and 1 post-Baseline PedACR30 assessment.

Change #100

Section 13.2.1 Data presentation, the following sentence has been added at the beginning of the paragraph:

For safety and efficacy analyses, study participants will be grouped by their Baseline weight strata (10 to <20kg [22 to <44lb], 20 to <40kg [44 to <88lb], and ≥40kg [≥88lb]). Selected analyses will also group study participants by their Baseline age group, concomitant MTX use, and anti-CZP antibody status.

Change #101

Section 13.2.2 Multicenter studies, the first sentence:

Approximately 70 centers are planned to enroll 125 study participants into this study.

Has been changed to:

Approximately 55 centers are planned to enroll 125 study participants into this study.

Change #102

Section 13.3 Planned safety analyses, the third paragraph:

Selected safety summaries will be presented overall as well as by age (2 to 5 years, 6 to 11 years, and 12 to 17 years) and weight strata (10 to <20kg [22 to <44lb], 20 to <40kg [44 to <88lb], and ≥40kg [≥88lb]) and study participants with or without concomitant MTX use. Safety summaries will be based upon the SS (study participants who were enrolled and took at least 1 dose of study medication).

Has been changed to:

Selected safety summaries will be presented overall and by Baseline weight strata, as well as by age (2 to 5 years, 6 to 11 years, and 12 to 17 years), by concomitant MTX use, and by anti-CZP antibody status. Safety summaries will be based upon the SS (study participants who were enrolled and took at least 1 dose of study medication).

Change #103

Section 13.5 Planned efficacy and health outcomes analyses, the fourth paragraph:

For PedACR30, PedACR50, PedACR70, and PedACR90, results will be presented overall as well as by age (2 to 4 years, 5 to 11 years, and 12 to 17 years) and weight strata (10 to <20kg [22 to <44lb], 20 to <40kg [44 to <88lb], and ≥40kg [≥88lb]) and study participants with or without concomitant MTX use.

Has been changed to:

For PedACR30, PedACR50, PedACR70, and PedACR90, results will be presented overall and by Baseline weight strata, as well as by age (2 to 5 years, 6 to 11 years, and 12 to 17 years), by concomitant MTX use, and by anti-CZP antibody status.

Change #104

Section 13.5 Planned efficacy and health outcomes analyses, the eighth bullet below the fourth paragraph has been removed:

- Shifts by visit of CRP from Baseline.

Change #105

Section 13.6 Handling of dropouts or missing data, the third paragraph, the first and second sentences:

Data collected after the taking of rescue medication will be treated as missing/non-response in all analyses except where specifically stated otherwise. See Section 7.8.2 for a list of medications which, if commenced after Week 16, would result in data at only the next scheduled visit (and not all subsequent visits) being treated as missing/non-response.

Has been changed to:

Data collected after the taking of rescue medication will be treated as missing for continuous efficacy endpoints and non-response for binary efficacy endpoints in all analyses except where specifically stated otherwise. See Section 7.8.2 for a list of medications which would

result in data at only the next scheduled visit (and not all subsequent visits) being treated as missing/non-response.

Change #106

Section 13.7 Planned interim analysis and data monitoring:

Following completion of Week 12 (Visit 7) by at least 20 study participants (minimum 6 study participants in each age group: 2 to 5 years, 6 to 11 years, and 12 to 17 years), PK data will be reviewed by age stratum and compared with plasma concentrations observed previously in adult study participants with RA. The plasma concentration analysis may be done in 2 or 3 stages if at least 20 study participants in total complete Week 12 (Visit 7) before 6 study participants in 1 or both of the other age groups have completed (see Section 5.1).

Comparisons will be made between the geometric mean and median values for the pediatric and adult study participants, as well as between the individual pediatric data and the adult 5th and 95th percentile and minimum and maximum observed values.

If the pediatric plasma concentrations demonstrate that the geometric mean and median concentrations are below the adult 5th percentile or above the 95th percentile, the PK data will be used to re-evaluate the weight-based dose adjustment algorithm for pediatric study participants. If necessary, a revised pediatric dose algorithm will be derived. Any change in dose regimen will require a protocol amendment prior to implementation.

Population PK or PK/PD analyses will not be performed separately on this initial 15-study participant cohort but later on the entire population.

After the last study participant has reached the Week 16 Visit (Visit 8, including collection of the Week 16 postdose blood samples), the database will be cut and a full interim analysis will be performed based upon 16 weeks of exposure for each individual (or all data for those cases who withdrew before this timepoint). This will be used to determine whether the study will continue or not. Given the descriptive nature of the data presentations, there are no statistical implications of this interim analysis.

A second full interim analysis will be performed upon 56 weeks of exposure (Visit 14) and will be used for the initial submission of results for regulatory purposes.

Further interim analyses may be performed at the Sponsor's discretion as required.

Has been changed to:

Interim analysis of PK data will compare CZP plasma concentration data from this study with CZP plasma concentrations observed previously in adult study participants with RA. This plasma concentration analysis will be done on an ongoing basis throughout the study, starting when 6 study participants in 1 of the age groups have completed Week 12 (Visit 7).

Comparisons will be made between the Week 12 geometric mean and median values for the pediatric and adult study participants, as well as between the individual pediatric data and the adult 5th and 95th percentile and minimum and maximum observed values.

If the pediatric plasma concentrations demonstrate that the geometric mean and median concentrations are below the adult 5th percentile or above the 95th percentile, the PK data will be used to re-evaluate the weight-based dose adjustment algorithm for pediatric study participants. Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicate that no change to the dosing algorithm is required. If future interim analyses, which may include PopPK, indicate that plasma levels of JIA study participants are outside of the exposure range observed in previous adult RA studies, a revised pediatric dose algorithm will be derived. Any change in dose regimen will require a protocol amendment prior to implementation.

After all active study participants have completed the Week 16 (Visit 8) assessments, an interim analysis of PedACR30 response rates will be performed and the study will be discontinued if less than 50% of the study population achieves a PedACR30 response at Week 16. Given the descriptive nature of the data presentations, there are no statistical implications of this interim analysis.

After the last study participant has reached the Week 24 Visit (Visit 10), the database will be cut and a full interim analysis of all safety and efficacy endpoints will be performed based upon 24 weeks of exposure for each individual (or all data for those cases who withdrew before this timepoint).

A second full interim analysis of all safety and efficacy endpoints will be performed based upon 56 weeks of exposure (Visit 14).

Further interim analyses may be performed at the Sponsor's discretion as required.

A DSMB will periodically review all emerging safety data. The DSMB members will be independent of the Sponsor and Investigators. The DSMB members will be informed by the Drug Safety representative (or designee) of all SAEs at the time of expedited reporting and will review periodically all emerging safety data (eg, SAEs, AEs, safety laboratory data). Based on the safety data, the DSMB can recommend modifying/stopping the study.

Change #107

Section 16 References, the following reference has been added:

Centers for Disease Control and Prevention. http:www.cdc.gov/TB/topic/testing/default.htm. Accessed 03 Sep 2012.

17.14 Protocol Amendment 4

Rationale for the amendment

The primary purpose of this substantial amendment is to implement a change in the dosing algorithm for children and adolescents currently enrolled in RA0043. A thorough review of all SAEs and AEs by the Safety Review Committee was performed and there were no unexpected safety findings. An interim PopPK analysis of CZP plasma concentration data from 35 study participants with post-Baseline samples in RA0043 was performed in combination with PK data from studies in Western (mainly Caucasian) adult study participants with RA and in Japanese adult study participants with RA. The interim PopPK analysis and subsequent simulations indicated that in all weight groups (10 to <20kg, 20 to <40kg, and ≥40kg), a higher exposure in terms of the maximum plasma concentration (C_{max}) and the area under the curve (AUC) is likely to be observed in the population of children and adolescents with the current dosing algorithm. This difference is not due to body mass/weight differences alone, and therefore an additional adjustment to the dosing algorithm to account for these unexplained differences is necessary in order to maintain children and adolescents within the adult exposure ranges. The clinical relevance in terms of efficacy or safety is currently unknown.

Based on the results of the interim PopPK analysis, new enrollment into RA0043 will be suspended, effective 17 Jul 2013, and the dose for study participants already enrolled in RA0043 will be reduced with Protocol Amendment 4. An overall dose reduction for pediatric study participants of 50% of the dose currently used in RA0043 is proposed to provide a pragmatic dosing regimen that will yield a closer match to the adult plasma concentration range achieved in adults with the approved label for RA (CZP 400mg at Weeks 0, 2, and 4 followed by CZP 200mg Q2W thereafter).

A summary table of the proposed revised dosing recommendations for loading and treatment doses in RA0043 based on the PopPK model simulations is provided below.

Table 17–1 Proposed revised dosing recommendation based on PopPK model simulations

Weight range	Loading dose (Weeks 0, 2, and 4)	Treatment dose (Week 6 and onwards)
10 to <20kg (22 to <44lb)	50mg Q2W	50mg Q4W
20 to <40kg (44 to <88lb)	100mg Q2W	50mg Q2W
≥40kg (≥88lb)	200mg Q2W	100mg Q2W

PopPK=population pharmacokinetic; Q2W=every 2 weeks; Q4W=every 4 weeks

The reduced loading dose will only apply to study participants already enrolled in RA0043 who do not achieve persistent CID and resume CZP treatment after implementation of Protocol Amendment 4.

A dose reduction of 50% can be implemented immediately by using the existing IMP without causing a study delay to acquire new drug supply. Following the change of dose, the ≥40kg (≥88lb) weight group will use the 0.5ml PFS (CZP 100mg) for treatment doses, while the 20

to <40kg (44 to <88lb) weight group will use the 0.25ml PFS (CZP 50mg) for treatment doses. As a PFS containing 25mg is not available, the lowest body weight category (10 to <20kg [22 to <44lb]) will use the 0.25ml PFS (CZP 50mg) administered with a 4-week dose interval.

Additional assessments of CZP plasma concentration after the change in dose have been added to the tabular schedule of study assessments to ensure that the 50% dose reduction will result in plasma concentrations within the target range of those observed in adults. Additional Unscheduled Visits have been implemented, as required, in order to closely monitor the study participants over a period of 12 weeks after the dose change.

In addition, changes have been made to clarify study-related procedures, and administrative and editorial changes have been made to update study personnel, update terminology, and correct errors.

Modifications and changes

Global changes

The following changes have been made throughout the protocol:

- The description of the dose regimen has been changed throughout the protocol to reflect the reduction of the treatment dose for study participants in the 3 weight categories.
- Additional PK samples after the dose change have been added throughout the protocol.
- The term "level" has been changed to "concentration" throughout the protocol for CZP plasma concentrations and antibody concentrations. This global change is not listed under the specific changes.
- The timing of predose and postdose vital sign assessments has been added throughout Section 8 for clarification, where applicable. This global change is not listed under the specific changes.
- The following clarification has been added in the description of timepoints for efficacy assessments in Section 11: "(including Unscheduled Visits that are related to the dose change implemented with Protocol Amendment 4)." This global change is not listed under the specific changes.

Specific changes

This section displays the modifications in this amendment compared with the previous version of the protocol dated 06 May 2013. The changes are displayed in the order of appearance.

Change #1

On the SPONSOR DECLARATION page, the name of the Clinical Program Director:

[redacted]

Has been changed to:

[redacted]

Change #2

Under STUDY CONTACT INFORMATION, the name and contact details of the Clinical Program Director:

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

Have been changed to:

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

Change #3

LIST OF ABBREVIATIONS, the following abbreviation:

Q2W	every 2 weeks

Has been changed to:

Q2W, Q4W	every 2 weeks, every 4 weeks

Change #4

Section 1 Summary, eighth paragraph, the first sentence:

Certolizumab pegol will be administered as a fixed dose based on weight every 2 weeks (Q2W) throughout the study consisting of 3 loading doses at Weeks 0, 2, and 4 (minimum=100mg, maximum=400mg) followed by a treatment dose (minimum=50mg, maximum=200mg).

Has been changed to:

Certolizumab pegol will be administered as a fixed dose based on weight throughout the study consisting of 3 loading doses at Weeks 0, 2, and 4 (minimum=50mg every 2 weeks [Q2W], maximum=200mg Q2W) followed by a treatment dose (minimum=50mg every 4 weeks [Q4W], maximum=100mg Q2W). With the implementation of Protocol Amendment 4, the reduced loading dose applies only for already enrolled study participants

who resume CZP treatment after nonpersistent Clinically Inactive Disease (CID). Prior to implementation of Protocol Amendment 4, the minimum and maximum loading doses in the study were CZP 100mg Q2W and CZP 400mg Q2W, respectively, and the minimum and maximum treatment doses were CZP 50mg Q2W and CZP 200mg Q2W, respectively.

Change #5

Section 1 Summary, eighth paragraph, the sixth and seventh sentences:

Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicate that no change to the dosing algorithm is required. If future analyses indicate that plasma levels of JIA study participants are outside of the exposure range observed in previous adult RA studies, the dosing algorithm may be changed via a protocol amendment.

Has been changed to:

Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future analyses indicate that plasma concentrations of JIA study participants are outside of the exposure range observed in previous adult RA studies, the dosing algorithm may be changed via a protocol amendment.

Change #6

Section 1 Summary, the following has been added below the eighth paragraph:

Results of an interim population pharmacokinetic (PopPK) analysis suggest that while observed CZP plasma concentrations have remained in the adult range, they have been at the upper end of the distribution. Simulations predict that for some study participants in RA0043 receiving the initially determined loading doses up to Week 4 (Visit 5), plasma concentrations are likely to exceed the range previously seen in adult study participants receiving CZP 400mg Q2W. Furthermore, plasma concentrations of study participants receiving the initially determined treatment dose after Week 4 (Visit 5) are predicted to exceed the concentration range observed in adults receiving CZP 200mg Q2W. Based on these findings, the dosing regimen will be changed with Protocol Amendment 4, and the doses to be administered will be reduced by 50% for all weight groups. This dose change is intended to achieve plasma concentrations that are similar to the effective concentrations observed in previous studies in adult study participants with RA. Additional assessments of the CZP plasma concentration after the change in dose will be performed to ensure that the 50% dose reduction will result in plasma concentrations within the target range of those observed in adults.

Change #7

Section 5.1 Study description, sixth paragraph, the second and third sentences:

Certolizumab pegol will be administered as a fixed dose based on weight, Q2W throughout the study (see Table 7-1). At Baseline (Week 0, Visit 2) eligible study participants will begin with 3 loading doses of CZP at Weeks 0, 2, and 4 (minimum=100mg, maximum=400mg) followed by a treatment dose for the duration of the study (minimum=50mg, maximum=200mg).

Has been changed to:

Certolizumab pegol will be administered as a fixed dose based on weight throughout the study (see Table 7-1). At Baseline (Week 0, Visit 2) eligible study participants will begin with 3 loading doses of CZP at Weeks 0, 2, and 4 (minimum=50mg Q2W, maximum=200mg Q2W) followed by a treatment dose for the duration of the study (minimum=50mg Q4W, maximum=100mg Q2W). With the implementation of Protocol Amendment 4, the reduced loading dose applies only for already enrolled study participants who resume CZP treatment after nonpersistent CID. Prior to implementation of Protocol Amendment 4, the minimum and maximum loading doses in the study were CZP 100mg Q2W and CZP 400mg Q2W, respectively, and the minimum and maximum treatment doses were CZP 50mg Q2W and CZP 200mg Q2W, respectively.

Change #8

Section 5.1 Study description, ninth paragraph, the second and third sentences:

Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicate that no change to the dosing algorithm is required. If future analyses indicate that plasma concentrations are outside of the exposure range observed in previous studies with adults, the dosing algorithm may be changed via a protocol amendment.

Have been changed to:

Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future analyses indicate that plasma concentrations are outside of the exposure range observed in previous studies with adults, the dosing algorithm may be changed via a protocol amendment.

Change #9

Section 5.1 Study description, the following has been added at the end of the section:

Results of an interim PopPK analysis conducted in Jun 2013 suggest that while observed CZP plasma concentrations have remained in the adult range, they have been at the upper end of the distribution. Simulations predict that for some study participants in RA0043 receiving the initially determined loading doses up to Week 4 (Visit 5), plasma concentrations are likely to exceed the range previously seen in adult study participants receiving CZP 400mg Q2W. Furthermore, plasma concentrations of study participants receiving the initially determined treatment dose after Week 4 (Visit 5) are predicted to exceed the concentration range observed in adults receiving CZP 200mg Q2W. Based on these findings, the dosing regimen will be changed with Protocol Amendment 4, and the doses to be administered will be reduced by 50% for all weight groups. This dose change is intended to achieve plasma concentrations that are similar to the effective concentrations observed in previous studies in adult study participants with RA. Additional assessments of the CZP plasma concentration after the change in dose will be performed to ensure that the 50% dose reduction will result in plasma concentrations within the target range of those observed in adults.

Change #10

Section 5.1.1 Study duration per study participant, the last line:

Planned Last Study participant, First Visit – 3Q/4Q 2013

Has been changed to:

Planned Last Study participant, First Visit – 3Q/4Q 2013 (to be confirmed)

Change #11

Section 5.2 Schedule of study assessments, footnotes "b," "u," "v," and "y" in Table 5-1:

[b] Vital signs, concomitant medications, concomitant procedures, and AEs must be assessed at every Unscheduled Visit. Other PK and safety assessments should be performed as related to nature of the visit.

[u] CZP plasma level and anti-CZP antibodies to be measured at Weeks 4, 12, 16, and 24. **A postdose CZP plasma sample will be collected at approximately 5 to 7 days following the Week 16 Visit (ie, requires an additional clinic site visit for blood collection at Week 17).**

[v] CZP plasma level and anti-CZP antibodies to be measured at Weeks 32, 40, and 48 and every 24 weeks thereafter.

[y] After Week 4 (Visit 5) study participants/caregivers may administer CZP Q2W at home between scheduled study visits. See Section 7.2 regarding training and option for continued site administration for site administration.

Have been changed to:

[b] Vital signs, concomitant medications, concomitant procedures, and AEs must be assessed at every Unscheduled Visit. Other PK and safety assessments should be performed as related to nature of the visit. For Unscheduled Visits related to the dose change with Protocol Amendment 4, see Sections 7.2.1 and 8.6.1. For these Unscheduled Visits, the same visit window applies, ie, ±3 days.

[u] CZP plasma concentration and anti-CZP antibodies to be measured at Weeks 4, 12, 16, and 24. **A postdose CZP plasma sample will be collected at approximately 5 to 7 days following the Week 16 Visit (ie, requires an additional clinic site visit for blood collection at Week 17).** For study participants already enrolled and treated prior to the implementation of Protocol Amendment 4 and hence undergoing a reduction of their dose, additional PK samples will be collected prior to dosing at the visit the dose change occurs and at the next 3 site visits following the dose change, ie, additional PK samples will be collected at the Unscheduled Visits or at the regular visits if not already planned per regular schedule. Afterwards, the regular PK sampling schedule applies.

[v] CZP plasma concentration and anti-CZP antibodies to be measured at Weeks 32, 40, and 48 and every 24 weeks thereafter. For study participants already enrolled and treated prior to the implementation of Protocol Amendment 4 and hence undergoing a reduction of their dose, additional PK samples will be collected prior to dosing at the visit the dose change occurs and at the next 3 site visits following the dose change, ie, additional PK samples will be collected at the Unscheduled Visits or at the regular visits if not already planned per regular schedule. Afterwards, the regular PK sampling schedule applies.

[y] After Week 4 (Visit 5) study participants/caregivers may administer CZP Q2W (or Q4W for the lowest weight group) at home between scheduled study visits. See Section 7.2 regarding training and option for continued site administration.

Change #12

Section 5.4.2 Dose selection, the third and fourth sentences in the paragraph below Table 5-2:

The intention is to study the equivalent dose regimen in children and adolescents, reducing the dose of CZP for pediatric study participants with body weights between 20 to <40kg (44 to <88lb) to CZP 200mg at Weeks 0, 2, and 4 followed by CZP 100mg Q2W (ie, 50% of the recommended adult dose). The dose of CZP will be reduced further to 25% of the adult dose for study participants with body weights 10 to <20kg (22 to <44lb) (ie, CZP 100mg at Weeks 0, 2, and 4 followed by CZP 50mg Q2W) (see Table 7-1).

Have been changed to:

The intention in RA0043 is to study the equivalent dose regimen in children and adolescents. Initial predictions, based on allometric scaling of PK data from adults, suggested that this could be achieved by reducing the dose of CZP for pediatric study participants with body weights between 20 to <40kg (44 to <88lb) to CZP 200mg at Weeks 0, 2, and 4 followed by CZP 100mg Q2W (ie, 50% of the recommended adult dose), and by reducing the dose further to 25% of the adult dose for study participants with body weights 10 to <20kg (22 to <44lb) (ie, CZP 100mg at Weeks 0, 2, and 4 followed by CZP 50mg Q2W). During the course of the study, results from the ongoing interim PK analysis and an interim PopPK analysis conducted in Jun 2013 indicated that plasma concentrations within the range previously seen in adult study participants receiving CZP 200mg Q2W would be achieved if the dose in RA0043 was reduced to 50%. Therefore, the treatment doses in this study will be reduced further with Protocol Amendment 4 so that study participants with body weights between 20 and <40kg (44 to <88lb) will receive CZP 50mg Q2W, and study participants with body weights of ≥40kg (≥88lb) will receive CZP 100mg Q2W (see Table 7-1). The optimal treatment dose estimated in the PopPK model for the lowest weight group would be CZP 25mg Q2W, however, the lowest available dose size is CZP 50mg. Thus, study participants with body weights of 10 to <20kg (22 to <44lb) will receive CZP 50mg Q4W to achieve a 50% reduction.

Change #13

Section 5.4.2 Dose selection, the paragraph at the end of the section:

The choice of dose and the weight-based dose-adjustment algorithm is supported by simulations of the PK exposure and response rates in children using the PopPK model and PK/PD exposure response model developed in adult RA study participants, corrected for pediatric demographics (C87079 addendum 08 Oct 2008). Results of these simulations show that all age groups exhibit similar exposures (C_{max} and AUC_T) to those of adults over the Week 14 to Week 16 dosing interval, with the pediatric/adult ratio of the median predicted values of PK parameters ranging from 1.03 to 1.19 for C_{max} and from 0.97 to 1.18 for AUC_T. The similarities in exposures are reflected in the probability of ACR20 response, which are similar for all age groups at Week 16 (pediatric/adult ratio of the median predicted values ranging from 1.08 to 1.10). These simulations were performed upon the assumption that disease progression and response rate for a given exposure are similar in children and adults.

Has been changed to:

The original choice of dose and the weight-based dose-adjustment algorithm, prior to Protocol Amendment 4, was supported by simulations of the PK exposure and response rates in children using the PopPK model and PK/PD exposure response model developed in adult RA study participants, corrected for pediatric demographics (C87079 addendum 08 Oct 2008). Results of these simulations showed that all age groups exhibit similar exposures (C_{max} and AUC_T) to those of adults over the Week 14 to Week 16 dosing interval, with the pediatric/adult ratio of the median predicted values of PK parameters ranging from 1.03 to 1.19 for C_{max} and from 0.97 to 1.18 for AUC_T. The similarities in exposures were reflected in the probability of ACR20 response, which are similar for all age groups at Week 16 (pediatric/adult ratio of the median predicted values ranging from 1.08 to 1.10). These simulations were performed upon the assumption that disease progression and response rate for a given exposure are similar in children and adults. The revised dose and weight-based dose adjustment algorithm was based on a PopPK analysis and simulation using data from 35 study participants in this study with post-Baseline plasma concentrations of CZP available prior to Protocol Amendment 4.

Change #14

Section 7.2 Treatments to be administered, first paragraph, the first sentence:

Throughout the study, CZP dosing is fixed dose based on weight and given Q2W.

Has been changed to:

Throughout the study, CZP dosing is fixed dose based on weight and given Q2W, with exception of the lowest weight group who will receive the treatment dose Q4W following implementation of Protocol Amendment 4.

Change #15

Section 7.2 Treatments to be administered, first paragraph, the third sentence:

Study participants start with 3 loading doses of CZP at Weeks 0, 2, and 4 (minimum=100mg, maximum=400mg) followed by a treatment dose for the duration of the study (minimum=50mg, maximum=200mg).

Has been changed to:

Study participants start with 3 loading doses of CZP at Weeks 0, 2, and 4 (minimum=50mg Q2W, maximum=200mg Q2W) followed by a treatment dose for the duration of the study (minimum=50mg Q4W, maximum=100mg Q2W). With the implementation of Protocol Amendment 4, the reduced loading dose applies only for already enrolled study participants who resume CZP treatment after nonpersistent CID.

Change #16

Section 7.2 Treatments to be administered, Table 7-1:

Table 7-1 Dosing administration of CZP

Weight range	Loading dose – Weeks 0, 2, and 4 (mg/kg dose range)	Treatment – Week 6 and onwards (mg/kg dose range)
10 to <20kg (22 to <44lb)	100mg (5-10mg/kg) 1 x 0.5mL inj	50mg (2.5-5mg/kg) 1 x 0.25 mL inj
20 to <40kg (44 to <88lb)	200mg (5-10mg/kg) 1 x 1mL inj	100mg (2.5-5mg/kg) 1 x 0.5mL inj
≥40kg (≥88lb)	400mg (<10mg/kg) 2 x 1mL inj	200mg (<5mg/kg) 1 x 1mL inj

CZP=certolizumab pegol; inj=injection

Note: A study participant should only change dosing category during the course of the study if their weight crosses the 40kg/88lb boundary due to a weight change of >5kg (11lb) (eg, a 39.0kg study participant becomes 44.1kg) or crosses the 20kg/44lb boundary due to a weight change of >2.5kg (5.5lb) (eg, a 19.0kg study participant becomes 21.6kg).

Has been changed to:

Table 7-1 Dosing administration of CZP[a]

Weight range	Loading dose – Weeks 0, 2, and 4[b] (mg/kg dose range)	Treatment – Week 6 and onwards (mg/kg dose range)
10 to <20kg (22 to <44lb)	50mg Q2W (2.5-5mg/kg) 1 x 0.25mL inj	50mg Q4W (2.5-5mg/kg) 1 x 0.25mL inj
20 to <40kg (44 to <88lb)	100mg Q2W (2.5-5mg/kg) 1 x 0.5mL inj	50mg Q2W (1.25-2.5mg/kg) 1 x 0.25mL inj
≥40kg (≥88lb)	200mg Q2W (<5mg/kg) 1 x 1mL inj	100mg Q2W (<2.5mg/kg) 1 x 0.5mL inj

CZP=certolizumab pegol; inj=injection; Q2W=every 2 weeks; Q4W=every 4 weeks

Note: A study participant should only change dosing category during the course of the study if their weight crosses the 40kg/88lb boundary due to a weight change of >5kg (11lb) (eg, a 39.0kg study participant becomes 44.1kg) or crosses the 20kg/44lb boundary due to a weight change of >2.5kg (5.5lb) (eg, a 19.0kg study participant becomes 21.6kg).

[a] Note that Table 7-1 describes the dosing administration of CZP after implementation of Protocol Amendment 4. Refer to Section 7.2.1 for the procedure to be taken for study participants already enrolled and treated prior to the implementation of Protocol Amendment 4, and who are undergoing a dose change.

[b] With implementation of Protocol Amendment 4, the reduced loading dose applies only for study participants who are already enrolled and who resume CZP treatment after nonpersistent Clinically Inactive Disease.

Change #17

Section 7.2 Treatments to be administered, the last sentence:

Study participants not achieving persistent CID and resuming treatment will re-start the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a treatment dose administered Q2W for the duration of the study (see Table 7-1).

Has been changed to:

Study participants not achieving persistent CID and resuming treatment will re-start the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a treatment dose administered Q2W, or Q4W for the lowest weight group after implementation of Protocol Amendment 4, for the duration of the study (see Table 7-1).

Change #18

A new subsection has been added at the end of Section 7.2 Treatments to be administered:

7.2.1 Procedure for dose change (Protocol Amendment 4)

With Protocol Amendment 4, the treatment dose in the study will be reduced by 50% for all weight groups.

- The timepoint of the dose change is the next scheduled time of injection after the Informed Consent form related to the dose change was signed. In case the next scheduled injection was planned for home dosing, the study participant will be requested to return to the clinic for an Unscheduled Visit for signing the Informed Consent form related to the dose change, administration of CZP, and to dispense the new supplies. Unused IMP dispensed previously needs to be returned.
  In case the study participant is not able to visit the site for that next scheduled injection, then the dose change must be performed at the next scheduled injection.
- Study participants will be monitored at least every 4 weeks over a period of 12 weeks after the dose change, either at the regularly scheduled visits or at additional Unscheduled Visits. The Unscheduled Visits will be scheduled to match with the dosing schedule, ie, the study medication will be administered at the day of the Unscheduled Visit. The Investigator should consult with the Medical Monitor in case of any questions related to the timing of the dose change or the Unscheduled Visits.
  - For study participants undergoing a dose change prior to or at Week 12 (Visit 8), and who return for regularly scheduled visits every 4 weeks for a period of 12 weeks after the dose change, no additional Unscheduled Visits will be required.
  - For study participants undergoing a dose change after Week 12 (Visit 8), 1 or 2 additional Unscheduled Visits will be required.
    For example, a study participant undergoing a dose change at Week 20 (Visit 9) will return for a regularly scheduled visit at Week 24 (Visit 10), will require an additional Unscheduled Visit at Week 28, and will return for the next regularly scheduled visit at Week 32 (Visit 11).
    A study participant who is undergoing a dose change at Week 40 (Visit 12) will require an Unscheduled Visit at Week 44, will return for a regularly scheduled visit at Week 48 (Visit 13), and will require another Unscheduled Visit at Week 52.
  - Study participants undergoing the dose change at an Unscheduled Visit between the regular visits will be required to return at the latest after 4 weeks for an Unscheduled Visit in case no regular visit is scheduled within 4 weeks. These study participants will then continue with the next regular visit as planned and return for a last Unscheduled Visit another 4 weeks later. For example, a study participant undergoing the dose change at Week 42 at the clinic will return for an Unscheduled Visit at Week 46, then continue with the regular visit at Week 48 (Visit 13), and return for an additional Unscheduled Visit at Week 52 before continuing with the regular Week 56 visit (Visit 14).
- At Unscheduled Visits when the dose change occurs and following the dose change, the following will be assessed: AEs, concomitant medications and procedures, vital signs, hematology/biochemistry, as well as CRP, PRINTO/PRCSG standard joint examination, Physician's Global Assessment of Disease Activity, CHAQ, and Parent's Global

Assessment of Overall Well-Being to determine PedACR response rates. Assessments at regular visits will be done as scheduled, except for PK sampling (see below).

- A predose PK sample will be collected prior to administration of CZP at the visit the dose change occurs. Additional predose PK sampling after the change in dose will be performed at the next 3 site visits, ie, additional PK samples will be collected at the Unscheduled Visits or at the regular visit if not already planned per regular schedule.

Change #19

Section 8.4 Visits 5 to 10 (Weeks 4, 8, 12, 16, 20, and 24), the 27th bullet point:

- CZP plasma levels and anti-CZP antibodies (Weeks 4, 12, 16, and 24 only; predose. Study participants will return to the clinic site for a **postdose CZP plasma sample** approximately **5 to 7 days following the Week 16 visit**.)

Has been changed to:

- CZP plasma concentrations and anti-CZP antibodies (Weeks 4, 12, 16, and 24 only, OR if a dose change is performed at the current visit OR if the study participant's dose was changed during 1 of the last 3 visits following Protocol Amendment 4; predose. Study participants will return to the clinic site for a **postdose CZP plasma sample** approximately **5 to 7 days following the Week 16 visit**.)

Change #20

Section 8.5 Visits 11 and continuing (Week 32 and every 8 weeks thereafter), the 27th bullet point:

- CZP plasma levels and anti-CZP antibodies (Weeks 32, 40, and 48 and every 24 weeks thereafter)

Has been changed to:

- CZP plasma concentrations and anti-CZP antibodies (Weeks 32, 40, and 48 and every 24 weeks thereafter, OR if a dose change is performed at the current visit OR if the study participant's dose was changed during 1 of the last 3 visits following Protocol Amendment 4)

Change #21

Section 8.6 Unscheduled Visit, the first bullet point:

- Vital signs

Has been changed to:

- Vital signs (within approximately 15 minutes prior to dosing and [pulse and blood pressure only] approximately 30 minutes after dosing, if dosing is applicable)

Change #22

Section 8.6 Unscheduled Visit, a new subsection has been added at the end of the section:

8.6.1 Unscheduled Visit related to dose change (Protocol Amendment 4)

If required, study participants will return for an Unscheduled Visit to undergo the dose change upon implementation of Protocol Amendment 4. Study participants will be monitored at least every 4 weeks over a period of 12 weeks after the dose change, either at the regularly scheduled visits or at additional Unscheduled Visits.

The following will be assessed at this visit:

- Administration of study medication
- CZP plasma concentrations and anti-CZP antibodies (predose)
- Adverse events
- Concomitant medications and procedures
- Vital signs (within approximately 15 minutes prior to dosing and [pulse and blood pressure only] approximately 30 minutes after dosing)
- Hematology/biochemistry
- CRP
- PRINTO/PRCSG standard joint examination
- Physician's Global Assessment of Disease Activity (VAS)
- CHAQ-parent reported
- Parent's Global Assessment of Overall Well-Being (VAS)
- IXRS contact, if applicable

Change #23

Section 9 Assessment of pharmacokinetics and immunological variables, the following has been added below the first paragraph:

For study participants already enrolled and treated prior to the implementation of Protocol Amendment 4 and hence undergoing a reduction of their dose, additional PK samples will be collected prior to dosing at the visit the dose change occurs and at the next 3 site visits following the dose change, ie, additional PK samples will be collected at either Unscheduled Visits or regular visits if not already planned per regular schedule. Afterwards, the regular PK sampling schedule applies.

Change #24

Section 9 Assessment of pharmacokinetics and immunological variables, fifth paragraph, the first and second sentences:

Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicate that no change to the dosing algorithm is required. If future analyses indicate that

plasma concentrations are outside of the exposure range of those observed in previous studies with adults, the dosing algorithm may be changed via a protocol amendment, and if necessary additional interim analyses including PopPK, may be performed.

Have been changed to:

Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future analyses indicate that plasma concentrations are outside of the exposure range of those observed in previous studies with adults, the dosing algorithm may be changed via a protocol amendment, and if necessary additional interim analyses including PopPK, may be performed.

Change #25

Section 9 Assessment of pharmacokinetics and immunological variables, the following has been added below the fifth paragraph:

Results of an interim PopPK analysis conducted in Jun 2013 suggest that while observed CZP plasma concentrations have remained in the adult range, they have been at the upper end of the distribution. Simulations predict that for some study participants in RA0043 receiving the initially determined loading doses up to Week 4 (Visit 5), plasma concentrations are likely to exceed the range previously seen in adult study participants receiving CZP 400mg Q2W. Furthermore, plasma concentrations of study participants receiving the initially determined treatment dose after Week 4 (Visit 5) are predicted to exceed the concentration range observed in adults receiving CZP 200mg Q2W. Based on these findings, the dosing regimen will be changed with Protocol Amendment 4, and the doses to be administered will be reduced by 50% for all weight groups. This dose change is intended to achieve plasma concentrations that are similar to the effective concentrations observed in previous studies in adult study participants with RA. Additional assessments of the CZP plasma concentration after the change in dose will be performed to ensure that the 50% dose reduction will result in plasma concentrations within the target range of those observed in adults.

Change #26

Section 10.6 Laboratory measurements, the following sentence has been added at the end of the first paragraph:

In addition, hematology, biochemistry, and CRP samples will be collected at Unscheduled Visits related to the dose change implemented with Protocol Amendment 4.

Change #27

Section 10.7.1 Vital signs, the last sentence:

Vital signs will be measured at Screening, Baseline, every visit through the Early Discontinuation/End of Treatment Visit, and the Final Visit 12 weeks after the last dose of study medication.

Has been changed to:

Vital signs will be measured at Screening, Baseline, every visit (including all Unscheduled Visits) through the Early Discontinuation/End of Treatment Visit, and the Final Visit 12 weeks after the last dose of study medication.

Change #28

Section 11.8 C-reactive protein (CRP), the third sentence:

Values will be used in determining PedACR clinical response, JADAS, CID and CRM, ratio to Baseline in CRP, and shift by visit of CRP from Baseline.

Has been changed to:

Values will be used in determining PedACR clinical response, JADAS, CID and CRM, and ratio to Baseline in CRP.

Change #29

Section 11.10 Clinically Inactive Disease and clinical remission, the last sentence:

Study participants not achieving persistent CID and resuming treatment will re-start the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a treatment dose administered Q2W for the duration of the study.

Has been changed to:

Study participants not achieving persistent CID and resuming treatment will re-start the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a treatment dose administered Q2W for the duration of the study, with exception of the lowest weight group, who will receive the treatment dose Q4W following implementation of Protocol Amendment 4.

Change #30

Section 13.4 Planned PK, PD, and immunological variable analysis, eighth paragraph, the second sentence:

Plasma concentration time curves will be plotted, overall, and by antibody status for each age stratum and the overall population.

Has been changed to:

Plasma concentration time curves will be plotted, overall, by Baseline age stratum, and by anti-CZP antibody status. Subgroup analyses will include an analysis of the study participants enrolled and treated up to the Week 16 timepoint under the original treatment dosing regimen.

Change #31

Section 13.7 Planned interim analysis and data monitoring, third paragraph, the second and third sentences:

Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicate that no change to the dosing algorithm is required. If future interim analyses, which may include PopPK, indicate that plasma levels of JIA study participants are outside of the exposure range observed in previous adult RA studies, a revised pediatric dose algorithm will be derived.

Have been changed to:

Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future interim analyses, which may include PopPK, indicate that plasma concentrations of JIA study participants are outside of the exposure range observed in previous adult RA studies, a revised pediatric dose algorithm will be derived.

Change #32

Section 13.7 Planned interim analysis and data monitoring, the following has been added below the third paragraph:

Based on results of an interim PopPK analysis conducted in Jun 2013 described in Section 5.1, the dosing regimen will be changed with Protocol Amendment 4, and the doses to be administered will be reduced by 50% for all weight groups. This change is intended to achieve plasma concentrations similar to the effective concentrations observed in previous studies in adult study participants with RA.

The CZP plasma concentrations will be monitored on an ongoing basis following the change in dose regimen to confirm they are within the adult range.

17.15 Protocol Amendment 5

Rationale for the amendment

The primary purpose of this substantial amendment is to reopen enrollment under the new reduced CZP dose regimen and to update the statistical analysis to account for the changes in the CZP dose regimen. FDA has agreed to the implementation of the reduced dosing regimen.

Two CZP dosing regimen subgroups will be defined as follows:

- Original CZP dose regimen: includes all study participants in the SS who began treatment in accordance with the original dosing regimen defined for the study (including study participants who underwent a dose reduction under Amendment 4).
- Reduced CZP dose regimen: includes all study participants in the SS who began treatment in accordance with the reduced dosing regimen defined for the study.

With implementation of Protocol Amendment 5, all newly enrolled study participants will receive loading and maintenance doses that correspond to 50% of the original CZP dose regimen used in RA0043. The maintenance dose of previously enrolled study participants was reduced with Protocol Amendment 4. The reduced CZP dose regimen as implemented with Protocol Amendments 4 and 5 is based on PopPK model simulations and is provided below.

Table 17–2 Proposed revised dosing recommendation based on PopPK model simulations

Weight range	Loading dose (Weeks 0, 2, and 4)	Maintenance dose (Week 6 and onwards)
10 to <20kg (22 to <44lb)	50mg Q2W	50mg Q4W
20 to <40kg (44 to <88lb)	100mg Q2W	50mg Q2W
≥40kg (≥88lb)	200mg Q2W	100mg Q2W

PopPK=population pharmacokinetic; Q2W=every 2 weeks; Q4W=every 4 weeks

At the time of Protocol Amendment 4, 78 study participants had been enrolled and started treatment on the original CZP dose regimen. To allow for a comparison of the group of 78 study participants on the original CZP dose regimen with a comparable group of study participants on the revised CZP dose regimen, a further 78 study participants are planned to be enrolled on the reduced CZP dose regimen. Thus, the overall number of study participants to be enrolled will be increased from 125 to 156. Study participants who had fulfilled the eligibility criteria but could not be enrolled due to the suspended enrollment as of 17 Jul 2013 will be allowed to be rescreened.

Key changes include the clarification that only study participants who will be enrolled under Protocol Amendment 5 and will begin treatment on the reduced CZP dose regimen will be taken into account for the study stopping rule based on the Week 16 PedACR30 interim analysis, and that a minimum number of 10 study participants in each weight category will need to be enrolled for the reduced CZP dose regimen.

In addition, the requirement that a study participant's dosing category may only be changed if the 40kg/88lb and 20kg/44lb weight boundaries are crossed due to weight changes of >5kg and >2.5kg, respectively, was removed from the protocol. Applying this requirement at the time of dose reduction would lead to potential underdosing of study participants who have just crossed the weight boundary, as they would have their doses reduced by 50% even though, based on their actual weight, they already fall into the next higher weight category.

Furthermore, additional changes have been made to the exclusion criteria and guidelines related to TB detection and monitoring to adapt the protocol to the current UCB standard, and descriptions of CID and CRM have been modified for clarity.

In addition, administrative and editorial changes have been made to update study personnel, update terminology, and to correct errors.

Modifications and changes

Global changes

The following changes have been made throughout the protocol and are not listed under the specific changes:

- The terms "treatment dose" and "Treatment Period" have been changed to "maintenance dose" and "Maintenance Period" throughout the protocol.
- The definition of the minimum number of study participants to be enrolled in each weight category has been updated throughout the protocol to clarify that a minimum number of 10 study participants on the reduced CZP dose regimen will be enrolled in each weight category. For the other enrollment categories (age categories, CZP monotherapy, study participants with ERA) the minimum enrollment numbers apply irrespective of the dose regimen.
- The definition of the study stopping rule has been updated throughout the protocol to clarify that the study will be discontinued if less than 50% of the study population enrolled on the reduced CZP dose regimen (Protocol Amendment 5) achieves a PedACR30 response at Week 16.
- The explanation that "With the implementation of Protocol Amendment 4, the reduced loading dose applies only for already enrolled study participants who resume CZP treatment after nonpersistent Clinically Inactive Disease (CID)" has been removed throughout the protocol as this is no longer applicable with implementation of Protocol Amendment 5.
- The description of minimum and maximum doses under the original CZP dose regimen has been updated to refer to both Protocol Amendments 4 and 5.
- The description that the dosing regimen will be changed based on findings from an interim PopPK analysis and the doses to be administered will be reduced by 50% for all weight groups has been updated throughout the protocol to refer to Protocol Amendments 4 and 5.

Specific changes

This section displays the modifications in this amendment compared with the previous version of the protocol dated 01 Aug 2013. The changes are displayed in the order of appearance.

Change #1

On the SPONSOR DECLARATION page, the name of the Study Physician:

[redacted]

Has been changed to:

[redacted]

Change #2

Under STUDY CONTACT INFORMATION, the name and contact details of the Study Physician:

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

Have been changed to:

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

Change #3

Under SERIOUS ADVERSE EVENT REPORTING, the global e-mail address:

DS_ICT@ucb.com

Has been changed to:

DSICT@ucb.com

Change #4

LIST OF ABBREVIATIONS, the following abbreviation has been added:

EAIR	exposure-adjusted incidence rate

Change #5

Section 1 Summary, fourth paragraph, the first sentence:

Approximately 167 study participants will be screened to enroll 125 study participants in this study.

Has been changed to:

Approximately 195 study participants will be screened to enroll 156 study participants in this study.

Change #6

Section 1 Summary, ninth paragraph, the last sentence:

Additional assessments of the CZP plasma concentration after the change in dose will be performed to ensure that the 50% dose reduction will result in plasma concentrations within the target range of those observed in adults.

Has been changed to:

Continued analysis of CZP plasma concentrations (including additional assessments for study participants undergoing a dose reduction with Protocol Amendment 4) will be performed to confirm that the 50% dose reduction will result in plasma concentrations within the target range of those observed in adults.

Change #7

Section 5.1 Study description, last paragraph, the last sentence:

Additional assessments of the CZP plasma concentration after the change in dose will be performed to ensure that the 50% dose reduction will result in plasma concentrations within the target range of those observed in adults.

Has been changed to:

Continued analysis of CZP plasma concentrations (including additional assessments for study participants undergoing a dose reduction with Protocol Amendment 4) will be performed to confirm that the 50% dose reduction will result in plasma concentrations within the target range of those observed in adults.

Change #8

Section 5.1.1 Study duration per study participant, the First Study participant, First Visit and Last Study participant, First Visit dates at the end of the section:

Planned First Study participant, First Visit – 1Q 2012

Planned Last Study participant, First Visit – 3Q/4Q 2013 (to be confirmed)

Have been changed to:

First Study participant, First Visit – 1Q 2012

Planned Last Study participant, First Visit – 1Q/2Q 2015

Change #9

Section 5.1.2 Planned number of study participants and sites, the first and second sentences:

Approximately 167 study participants will be screened at about 55 centers in order to enroll 125 study participants in this study.

The enrollment per site is limited to a maximum of 10 study participants.

Have been changed to:

Approximately 195 study participants will be screened at about 55 centers in order to enroll 156 study participants in this study.

The enrollment per site is limited to a maximum of 12 study participants.

Change #10

Section 5.4.2 Dose selection, the paragraph below Table 5-2 (fifth sentence onwards):

During the course of the study, results from the ongoing interim PK analysis and an interim PopPK analysis conducted in Jun 2013 indicated that plasma concentrations within the range previously seen in adult study participants receiving CZP 200mg Q2W would be achieved if the dose in RA0043 was reduced to 50%. Therefore, the treatment doses in this study will be reduced further with Protocol Amendment 4 so that study participants with body weights between 20 and <40kg (44 to <88lb) will receive CZP 50mg Q2W, and study participants with body weights of ≥40kg (≥88lb) will receive CZP 100mg Q2W (see Table 7-1). The optimal treatment dose estimated in the PopPK model for the lowest weight group would be CZP 25mg Q2W, however, the lowest available dose size is CZP 50mg. Thus, study participants with body weights of 10 to <20kg (22 to <44lb) will receive CZP 50mg Q4W to achieve a 50% reduction.

Has been changed to:

During the course of the study, results from the ongoing interim PK analysis and an interim PopPK analysis conducted in Jun 2013 indicated that plasma concentrations within the range previously seen in adult study participants receiving CZP 200mg Q2W would be achieved if the dose in RA0043 was reduced to 50% of the original dose used in the study. Therefore, the maintenance doses in this study will be reduced further with Protocol Amendment 4 so that study participants with body weights between 20 and <40kg (44 to <88lb) will receive CZP 50mg Q2W, and study participants with body weights of ≥40kg (≥88lb) will receive CZP 100mg Q2W (see Table 7-1). The optimal maintenance dose estimated in the PopPK model for the lowest weight group would be CZP 25mg Q2W, however, the lowest available dose size is CZP 50mg. Thus, study participants with body weights of 10 to <20kg (22 to <44lb) will receive CZP 50mg Q4W to achieve this 50% reduction. In addition, with Protocol Amendment 5, the loading dose in the study will be reduced by 50% for newly enrolled study participants, so that study participants with body weights of 10 to <20kg (22 to <44lb) will

receive CZP 50mg at Weeks 0, 2, and 4, study participants with body weights between 20 to <40kg (44 to <88lb) will receive CZP 100mg at Weeks 0, 2, and 4, and study participants with body weights ≥40kg (≥88lb) will receive CZP 200mg at Weeks 0, 2, and 4.

Change #11

Section 6.2 Exclusion criteria, exclusion criterion no. 11, the first sentence:

11. Study participants with known TB infection, at high risk of acquiring TB infection, or latent TB (LTB) infection are excluded:

Has been changed to:

11. Study participants with known TB infection, or at high risk of acquiring TB infection, are excluded. Study participants with latent TB (LTB) infection that have not received a minimum of 4 weeks of prophylactic treatment are only eligible following prophylaxis:

Change #12

Section 6.2 Exclusion criteria, exclusion criterion no. 11, the first sentence under "c":

c. Latent TB infection (unless appropriate prophylaxis is initiated prior to study treatment according to Section 10.7.9.1.1 and continued to completion of prophylaxis) is defined as:

Has been changed to:

c. Latent TB infection is defined as:

Change #13

Section 6.3 Retesting and rescreening, second paragraph, the following has been added as a new bullet below the first bullet:

- Study participants who fulfilled all eligibility criteria but were registered as Screen failures due to suspension of enrollment as of 17 Jul 2013 are allowed to be rescreened.

Change #14

Section 6.4 Withdrawal criteria, withdrawal criterion no.3:

3. Study participant who develops confirmed reactivation of latent or active TB or NTMB infection during the study (including, but not limited to, conversion demonstrated by IGRA or PPD or other diagnostic means, eg, TB questionnaire, during the course of the study) must be withdrawn.

Has been changed to:

3. Study participant who develops active TB or NTMB infection during the study must be withdrawn.

Change #15

Section 7.2 Treatments to be administered, the second paragraph:

To prevent unnecessary switching of study participants between weight categories, a study participant's dosing category may only be changed after assessment of weight changes by the

Investigator at a scheduled clinic visit **and** if their weight crosses the 40kg/88lb boundary due to a weight change of >5kg (11lb) compared to their last weight measurement of the lower weight category (eg, a 39.0kg study participant becomes 44.1kg) or crosses the 20kg/44lb boundary due to a weight change of >2.5kg (5.5lb) (eg, a 19.0kg study participant becomes 21.6kg). Weight, weight change, and any change in study medication dose will be documented.

Has been changed to:

A study participant's dosing category will only be changed after the confirmation of a weight change by the Investigator **at a scheduled clinic visit.**

The study participant will receive the dose of the next weight category once their weight crosses the 40kg/88lb boundary or crosses the 20kg/44lb boundary at a scheduled clinic visit. The study participant will continue on the dose of the new weight category regardless of potential decrease of the weight below the boundary. In case of significant weight fluctuations the Investigator should contact the Medical Monitor to discuss and confirm potential change in dosing if medically advised or discontinuation of treatment (eg, if related to AE).

Change #16

Section 7.2 Treatments to be administered, the note below Table 7-1:

Note: A study participant should only change dosing category during the course of the study if their weight crosses the 40kg/88lb boundary due to a weight change of >5kg (11lb) (eg, a 39.0kg study participant becomes 44.1kg) or crosses the 20kg/44lb boundary due to a weight change of >2.5kg (5.5lb) (eg, a 19.0kg study participant becomes 21.6kg).

Has been changed to:

Note: A study participant should change dosing category during the course of the study if their weight crosses the 40kg/88lb boundary or crosses the 20kg/44lb boundary.

Change #17

Section 7.2 Treatments to be administered, the last paragraph:

Study participants achieving clinical remission on medication (CRM), ie, after 6 months of CID, may discontinue CZP treatment at the Investigator's discretion following consultation with the Sponsor to confirm remission status. Study participants will remain in the study and continue with scheduled study visits. Study participants not achieving persistent CID will be allowed to resume CZP treatment at any time at the Investigator's discretion. If a study participant is on concomitant MTX treatment, the Investigator may decide to decrease and ultimately discontinue the MTX dose after complete discontinuation of CZP. Study participants not achieving persistent CID and resuming treatment will re-start the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a treatment dose administered Q2W, or Q4W for the lowest weight group after implementation of Protocol Amendment 4, for the duration of the study (see Table 7-1).

Has been changed to:

Study participants achieving clinical remission on medication (CRM), ie, after 6 months of continuous CID, may discontinue CZP treatment at the Investigator's discretion following consultation with the Sponsor to confirm remission status. Study participants who have discontinued CZP due to achieving CRM will be allowed to remain in the study and continue with scheduled study visits. Study participants not maintaining persistent CID following achievement of CRM will be allowed to resume CZP treatment at any time at the Investigator's discretion and consultation with the Sponsor. If a study participant is on concomitant MTX treatment, the Investigator may decide to decrease and ultimately discontinue the MTX dose after complete discontinuation of CZP. Study participants not maintaining persistent CID following achievement of CRM and resuming treatment will restart the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a maintenance dose administered Q2W, or Q4W for the lowest weight group after implementation of Protocol Amendment 4, for the duration of the study (see Table 7-1).

Change #18

Section 7.2.1 Procedure for dose change (Protocol Amendment 4), the first sentence:

With Protocol Amendment 4, the treatment dose in the study will be reduced by 50% for all weight groups.

Has been changed to:

With Protocol Amendment 4, the maintenance dose in the study will be reduced by 50% for all weight groups (not applicable for study participants enrolled on the reduced CZP dose regimen per Protocol Amendment 5).

Change #19

Section 7.8.1 Permitted concomitant treatments (medications and therapies), first bullet "MTX, if being used" the fourth and fifth points in the list:

- During the study, the MTX dose may be decreased, but not discontinued. Methotrexate may be discontinued only for documented reasons of intolerance or toxicity, or in study participants who achieve CRM and only after discontinuation of CZP.
- Study participants who do not achieve persistent CRM status can reinitiate therapy with MTX.

Have been changed to:

- During the study, the MTX dose may be decreased, but not discontinued. Methotrexate may be discontinued only for documented reasons of intolerance or toxicity, or in study participants who achieve CRM (persistent CID over a period of 6 months, as defined in Section 11.10) and only after discontinuation of CZP.
- Study participants who do not maintain persistent CID following achievement of CRM can reinitiate therapy with MTX.

Change #20

Section 9 Assessment of pharmacokinetics and immunological variables, sixth paragraph, the last sentence:

Additional assessments of the CZP plasma concentration after the change in dose will be performed to ensure that the 50% dose reduction will result in plasma concentrations within the target range of those observed in adults.

Has been changed to:

Continued analysis of CZP plasma concentrations (including additional assessments for study participants undergoing a dose reduction with Protocol Amendment 4) will be performed to confirm that the 50% dose reduction will result in plasma concentrations within the target range of those observed in adults.

Change #21

Section 10.1.8 Ongoing safety data review and oversight, second paragraph, the fourth sentence:

In addition, a Data and Safety Monitoring Board (DSMB) will periodically review all emerging safety data (see Section 13.7).

Has been changed to:

In addition, a Data and Safety Monitoring Board (DSMB) will periodically review emerging safety and efficacy data (see Section 13.7).

Change #22

Section 10.7.9.1.1 Latent tuberculosis infection, the first and second sentences:

Per exclusion criterion 11c, LTB infection is defined as a positive TB test (IGRA or PPD) and chest imaging without positive findings for TB along with the absence of signs, symptoms, or physical findings suggestive of TB infection. If available, smears and cultures of secretions or tissues should also be negative.

Have been changed to:

Latent TB infection is defined as a positive TB test (IGRA or PPD) and chest imaging without positive findings for TB along with the absence of signs, symptoms, or physical findings suggestive of TB infection. If available, smears and cultures of secretions or tissues should also be negative (refer to exclusion criterion 11c).

Change #23

Section 10.7.9.1.1 Latent tuberculosis infection, the fourth sentence:

Study participants who have received prophylactic therapy for LTB infection for at least 4 weeks prior to enrollment (initiation of CZP treatment at Baseline) and are committed to completing the full course of therapy, may be considered for study participation.

Has been changed to:

Study participants who have received prophylactic therapy for LTB infection for at least 4 weeks prior to initiation or continuation of CZP treatment and who are committed to completing the full course of therapy, may be considered for study participation or can continue on the study.

Change #24

Section 10.7.9.1.1 Latent tuberculosis infection, the text under "**LTB infection and active TB identified during study**":

During the study, study participants who develop evidence of LTB infection or active TB must immediately discontinue further administration of IMP, be scheduled for the Early Discontinuation Visit and Final Visit, and referred to a TB specialist for evaluation. Evidence of LTB infection is defined as study participant's IGRA test converts to positive or indeterminate (and confirmed indeterminate on repeat), or PPD converts to positive (this only applies for regions or sites where UCB has determined PPD may be used for screening and follow-up), or the study participant's questionnaire or history and physical examination indicates that TB infection or exposure may have occurred. Evidence of active TB includes, in addition to the aforementioned tests, signs and symptoms of organ involvement. In either situation, the study participant should be carefully assessed by a TB specialist for active TB (see Section 10.7.9.1). Study participants diagnosed with active TB or LTB infection should receive appropriate TB or prophylaxis therapy respectively per local and UCB guidelines as described above. Any presumptive diagnosis or diagnosis of LTB infection or active TB is a reportable event; refer to Section 10.2.2 for details. The Investigator is to complete and submit the TB follow-up form provided.

The study participant should be transferred to the care of their physician and managed according to the best available standard of care. Study participants identified as having converted to LTB infection or active TB during the study must be scheduled to return for the Early Discontinuation Visit as soon as possible but no later than the next scheduled study visit. The study participant should be encouraged to keep the Final Visit as specified by the protocol.

If infection with NTMB is identified during the study, the same procedure as for active TB acquired during the study must be followed.

Has been changed to:

During the study, study participants who develop evidence of LTB infection or active TB must immediately stop further administration of study medication and be referred to an appropriate TB specialist (pulmonologist and infectious disease specialist) for further evaluation (see Section 10.7.9.1). Evidence of LTB infection is defined as study participant's IGRA test converts to positive or indeterminate (and confirmed indeterminate on repeat), or PPD converts to positive, or the study participant's questionnaire or history and physical examination indicates that TB infection or exposure may have occurred. Evidence of active TB includes, in addition to the aforementioned tests, signs and symptoms of organ involvement. In either situation, the study participant should be carefully assessed by a TB

specialist for active TB. Study participants diagnosed with active TB or LTB infection should receive appropriate TB or prophylaxis therapy. In case a TB specialist excludes an active TB the study participant can proceed with the study medication no earlier than 4 weeks after the start of an appropriate prophylactic therapy.

Any presumptive diagnosis or diagnosis of a TB infection is a reportable event, and confirmed active TB has to be reported as an SAE (please see Section 10.2.2 Procedures for reporting SAEs for details). The Investigator is to complete and submit the TB follow-up form provided.

The study participant should be transferred to the care of their physician and managed according to the best available standard of care. Study participants identified as having converted to active TB during the study must be withdrawn and scheduled to return for the Early Discontinuation Visit as soon as possible but no later than the next scheduled study visit.

The study participant should be encouraged to complete the Final Visit 12 weeks after the last dose of study medication.

If infection with NTMB is identified during the study, the same procedure as for active TB acquired during the study must be followed.

Study participants with LTB infection must not undergo repeat PPD and IGRA testing. The PPD and IGRA test should be used for any protocol mandated monitoring.

Follow-up information of suspected and confirmed TB cases should be provided to UCB at least after 3, 9, and 12 months of start date of anti-TB treatment, including hematological and biochemical safety parameters, x-ray evolution data, and TB diagnostic procedures used to follow up and confirm recovery of TB.

Change #25

Section 11.10 Clinically Inactive Disease and clinical remission, the last paragraph:

Study participants achieving CRM, ie, after 6 months of CID, may discontinue CZP treatment at the Investigator's discretion following consultation with the Sponsor to confirm remission status. Study participants will remain in the study and continue with scheduled study visits. Study participants not achieving persistent CID will be allowed to resume CZP treatment at any time at the Investigator's discretion. If a study participant is on concomitant MTX treatment, the Investigator may decide to decrease and ultimately discontinue the MTX dose after complete discontinuation of CZP. Study participants not achieving persistent CID and resuming treatment will restart the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a treatment dose administered Q2W for the duration of the study, with exception of the lowest weight group, who will receive the treatment dose Q4W following implementation of Protocol Amendment 4.

Has been changed to:

Study participants achieving CRM, ie, after 6 months of continuous CID, may discontinue CZP treatment at the Investigator's discretion following consultation with the Sponsor to

confirm remission status. Study participants who have discontinued CZP due to achieving CRM will be allowed to remain in the study and continue with scheduled study visits. Study participants not maintaining persistent CID following achievement of CRM will be allowed to resume CZP treatment at any time at the Investigator's discretion and consultation with the Sponsor. If a study participant is on concomitant MTX treatment, the Investigator may decide to decrease and ultimately discontinue the MTX dose after complete discontinuation of CZP. Study participants not maintaining persistent CID following achievement of CRM and resuming treatment will restart the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a maintenance dose administered Q2W for the duration of the study, with exception of the lowest weight group, who will receive the maintenance dose Q4W following implementation of Protocol Amendment 4.

Change #26

Section 13.2.1 Data presentation, the following has been added at the end of the first paragraph:

Subgroups defined by CZP dosing regimen will also be displayed. Two CZP dosing regimen subgroups will be defined as follows:

- Original CZP dose regimen: includes all study participants in the SS who began treatment in accordance with the original dosing regimen defined for the study (3 loading doses of CZP at Weeks 0, 2, and 4 [minimum=100mg Q2W, maximum=400mg Q2W] followed by a maintenance dose for the duration of the study [minimum=50mg Q2W, maximum=200mg Q2W]). This subgroup includes all study participants who began the study with this CZP dose regimen and received 1 or more doses of this regimen, regardless of any subsequent switch to the reduced CZP dose regimen.
- Reduced CZP dose regimen: includes all study participants in the SS who began treatment in accordance with the reduced dosing regimen defined for the study (3 loading doses of CZP at Weeks 0, 2, and 4 [minimum=50mg Q2W, maximum=200mg Q2W] followed by a maintenance dose for the duration of the study [minimum=50mg Q4W, maximum=100mg Q2W]).

Change #27

Section 13.2.2 Multicenter studies:

Approximately 55 centers are planned to enroll 125 study participants into this study. The enrollment per site is limited to a maximum of 10 study participants.

Has been changed to:

Approximately 55 centers are planned to enroll 156 study participants into this study. The enrollment per site is limited to a maximum of 12 study participants.

Change #28

Section 13.3 Planned safety analyses:

The incidence of AEs will be assessed as primary safety variable in this study.

Safety summaries will include presentations of AEs, extent of exposure, laboratory values (hematology and biochemistry), vital signs, concomitant medications and procedures, and autoantibody (ANA and anti-dsDNA antibodies) concentrations. Urinalysis results will be listed. Tanner stages will be presented by category. Growth as measured by height and weight will be assessed in relation to a comparative population and this may include an assessment of any change after treatment with CZP.

Selected safety summaries will be presented overall and by Baseline weight strata, as well as by age (2 to 5 years, 6 to 11 years, and 12 to 17 years), by concomitant MTX use, and by anti-CZP antibody status. Safety summaries will be based upon the SS (study participants who were enrolled and took at least 1 dose of study medication).

Has been changed to:

The incidence of AEs will be assessed as primary safety variable in this study. The primary summaries of safety will include all study participants in the SS, regardless of CZP dose. Safety variables will be summarized overall and separately for the 2 CZP dose regimens (original CZP dose regimen, reduced CZP dose regimen).

Safety summaries will include presentations of AEs, extent of exposure, laboratory values (hematology and biochemistry), vital signs, concomitant medications and procedures, and autoantibody (ANA and anti-dsDNA antibodies) concentrations. Urinalysis results will be listed. Tanner stages will be presented by category. Growth as measured by height and weight will be assessed in relation to a comparative population and this may include an assessment of any change after treatment with CZP.

For AEs, the exposure-adjusted incidence rate (EAIR) will also be calculated. For EAIR, the numerator will be the total number of study participants experiencing a particular AE. The denominator will be study participant-years, ie, the total summation of individual study participant-years at risk up to the first occurrence of the given AE for study participants with that AE, plus the total study participant-years at risk for those study participants not experiencing that AE.

For the original CZP dose regimen subgroup, in addition to the overall presentation of AEs, AEs will be summarized separately for the periods of exposure to original and reduced CZP dose regimens. Additionally, the frequency and percentage of AEs reported during the first 16 weeks of study medication exposure will be summarized separately for the 2 CZP dose regimens (original CZP dose regimen, reduced CZP dose regimen). This analysis will be repeated, excluding any study participants who switched from the original to the reduced CZP dose regimen prior to Week 16. Selected safety summaries will be presented overall and by Baseline weight strata, as well as by age (2 to 5 years, 6 to 11 years, and 12 to 17 years), by concomitant MTX use, and by anti-CZP antibody status.

Change #29

Section 13.4 Planned PK, PD, and immunological variable analysis, the third and fourth paragraphs:

In the Bayesian approach, the distributions of PK parameters estimated from adult data (from the PopPK analysis in C87068) will be incorporated as prior information in the model to

estimate pediatric PK parameters. This combination of prior knowledge and sparse pediatric data will be analyzed within Winbugs.

The meta-analysis will be performed by adding the pediatric data to the adult data that were previously used to perform the adult PopPK analysis within NONMEM (C87068).

Have been changed to:

In the Bayesian approach, the distributions of PK parameters estimated from adult data (from the PopPK analysis in C87068 and CL0153) will be incorporated as prior information in the model to estimate pediatric PK parameters. This combination of prior knowledge and sparse pediatric data will be analyzed within Winbugs.

The meta-analysis will be performed by adding the pediatric data to the adult data that were previously used to perform the adult PopPK analysis within NONMEM (C87068 and CL0153).

Change #30

Section 13.4 Planned PK, PD, and immunological variable analysis, the eighth paragraph:

Certolizumab pegol plasma concentration data will be tabulated and summarized for each visit on which samples were taken (geometric mean, arithmetic mean, minimum, maximum, standard deviation and % coefficient of variation). Plasma concentration time curves will be plotted, overall, by Baseline age stratum, and by anti-CZP antibody status. Subgroup analyses will include an analysis of the study participants enrolled and treated up to the Week 16 timepoint under the original treatment dosing regimen.

Has been changed to:

Certolizumab pegol plasma concentration data will be tabulated and summarized by dose regimen (original CZP dose regimen or reduced CZP dose regimen) for each visit on which samples were taken (geometric mean, arithmetic mean, minimum, maximum, standard deviation and % coefficient of variation). Plasma concentration time curves will be plotted separately for study participants who began treatment according to the original CZP dose regimen or the reduced CZP dose regimen, overall, by Baseline age stratum, and by anti-CZP antibody status. Subgroup analyses will include an analysis of the study participants enrolled and treated up to the Week 16 timepoint under the original maintenance dosing regimen.

Change #31

Section 13.5 Planned efficacy and health outcomes analyses, the following has been added below the first paragraph:

All efficacy and health outcomes variables results will be presented overall and separately for the 2 CZP dose regimens (original CZP dose regimen, reduced CZP dose regimen).

Change #32

Section 13.7 Planned interim analysis and data monitoring, the fifth paragraph:

The CZP plasma concentrations will be monitored on an ongoing basis following the change in dose regimen to confirm they are within the adult range.

Has been changed to:

The CZP plasma concentrations will be monitored on an ongoing basis following the change in dose regimen to confirm they are within the targeted adult range.

Change #33

Section 13.7 Planned interim analysis and data monitoring, the last paragraph:

A DSMB will periodically review all emerging safety data. The DSMB members will be independent of the Sponsor and Investigators. The DSMB members will be informed by the Drug Safety representative (or designee) of all SAEs at the time of expedited reporting and will review periodically all emerging safety data (eg, SAEs, AEs, safety laboratory data). Based on the safety data, the DSMB can recommend modifying/stopping the study.

Has been changed to:

A DSMB will periodically review emerging safety and efficacy data. The DSMB members will be independent of the Sponsor and Investigators. The DSMB members will be informed by the Drug Safety representative (or designee) of all SAEs at the time of expedited reporting and will periodically review emerging safety data (eg, SAEs, AEs, safety laboratory data) and efficacy data, as applicable, during the course of the study. Based on the safety data, the DSMB can recommend modifying/stopping the study.

Change #34

Section 13.8 Determination of sample size, the first paragraph:

Based upon the ICH guideline for the assessment of safety, it is planned to enroll a sufficient number of study participants to this study to have a minimum of 100 with at least 12 months continuous exposure to CZP. Assuming a dropout rate of approximately 20%, this means that 125 study participants would need to be enrolled. Further assuming a Screening failure rate of 25%, it is planned to screen 167 study participants.

Has been changed to:

Based upon the ICH guideline for the assessment of safety, it is planned to enroll a sufficient number of study participants to this study to have a minimum of 100 with at least 12 months continuous exposure to CZP. Assuming a dropout rate of approximately 20%, it was originally determined that 125 study participants would need to be enrolled. At the time of Protocol Amendment 5, 78 study participants had been enrolled according to the original CZP dose regimen, and it is planned to enroll a further 78 study participants on the reduced CZP dose regimen, so that a comparable number of study participants on the reduced CZP dose regimens can be analyzed. Thus, the total number of study participants planned to be enrolled will be increased to 156 study participants. Assuming a Screening failure rate of 25%, it is planned to screen 195 study participants in total.

Change #35

Section 13.8 Determination of sample size, second paragraph, the first sentence:

Simulations using the adult population PK model in pediatric study participants with JIA suggest that the planned sample size of 125 study participants is adequate for PK assessment purposes.

Has been changed to:

Prior to the start of study conduct, simulations using the adult population PK model in pediatric study participants with JIA suggested that the planned sample size of 125 study participants was adequate for PK assessment purposes.

Change #36

Section 13.8 Determination of sample size, the following has been added at the end of the section:

Data from all 156 study participants will be included in the final PopPK analysis, and therefore should allow CL/F and V/F to be determined with sufficient precision.

17.16 Protocol Amendment 6

Rationale for the amendment

The primary purpose of this **administrative** amendment is to update the packaging and labeling sections of the protocol to account for a new presentation of the prefilled syringe (PFS).

In addition, administrative changes have been made to move the Sponsor declaration page to the back of the document to comply with the new electronic signature process, to update study personnel, and to correct typographical errors.

Modifications and changes

Global change

The terms "Treatment Period" and treatment dose" were changed globally to "Maintenance Period" and "maintenance dose " with RA0043 Protocol Amendment 5. However, in text that refers to the overall open-label Treatment Period in the study, which includes a Loading and a Maintenance Period, the term "Treatment Period" should still be used. This has been corrected throughout the protocol.

Specific changes

This section displays the modifications in this amendment compared with the previous version of the protocol dated 20 Jan 2014. The changes are displayed in the order of appearance.

Change #1

The SPONSOR DECLARATION page was removed from page 2 and added as a new section at the back of the document:

19 SPONSOR DECLARATION

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

Change #2

Under STUDY CONTACT INFORMATION, contact details of the Study Physician:

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

Have been changed to:

Name:	[redacted]
Address:	Chemin du Foriest B - 1420 Braine-l'Alleud Belgium
Phone:	[redacted]
Fax:	

Change #3

Under STUDY CONTACT INFORMATION, contact details of the Clinical Trial Biostatistician:

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

Have been changed to:

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

Change #4

LIST OF ABBREVIATIONS, the following abbreviation has been added:

GMP	Good Manufacturing Practice

Change #5

Section 7.3 Packaging:

Each site will receive uniquely numbered PFS of CZP 200mg/mL. The PFS will be packaged in individual protective containers (clamshell). Each clamshell will be packaged in an individual carton.

The site will contact the IXRS at each visit in order to obtain the PFS number(s) (MED ID) to be dispensed to a specific study participant.

Has been changed to:

Certolizumab pegol is packaged and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. They are suitably packaged in such a way as to protect the IMPs from deterioration during transport and storage.

Change #6

Section 7.4 Labeling:

Clinical drug supplies will be labeled in accordance with the current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. Where necessary, labels will be translated into the local language.

All PFS will be inserted into a labeled individual container (clamshell). The label of an individual container has 2 sections. The tear-off section will be removed and attached to the source document at the time of study medication administration to the study participant and the main section will remain affixed to the individual container.

Prefilled syringes used for administration will be labeled with the same unique identifier (MED ID) as on the individual container. Cartons containing the clamshells will also be labeled with the same unique identifier (MED ID) as on the individual container.

Name, address, and phone number of the Investigator will be included on the study participant identification card (see Section 14.2).

Has been changed to:

Clinical drug supplies will be labeled in accordance with the current International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language. Details on Labeling will be provided in the Pharmacy manual.

17.17 Protocol Amendment 7

Rationale for the amendment

The primary purpose of this substantial amendment is to update the protocol in accordance with current UCB TB detection procedures, including the introduction of yearly TB testing and the extension of the prophylactic TB treatment duration from 4 to 8 weeks. Furthermore, it has been clarified that long-term efficacy data from study participants who withdraw from the study after Week 56 or initiate any rescue medication use after Week 56 will be analyzed "as observed" and will no longer be imputed as nonresponse or missing.

Moreover, a section on "Suspected transmission of an infectious agent via a medicinal product" has been added in accordance with current company standards.

In addition, study contact details have been updated and minor clarifications have been made.

Modifications and changes

Global changes

The following changes have been made throughout the protocol:

- Yearly TB testing and prophylactic TB treatment duration of 8 weeks have been implemented. Of note, no changes have been made to the eligibility criteria in Section 6 (eg, Exclusion Criterion #11) and the description of Screening procedures for TB infection at study entry (Section 10.7.9.1.1) because enrollment in the study is complete at the time of this protocol amendment.
- References to UCB Drug Safety have been changed to UCB Patient Safety.

Specific changes

This section displays the modifications in this amendment compared with the previous version of the protocol dated 17 Sep 2015. The changes are displayed in the order of appearance.

Change #1

Under SERIOUS ADVERSE EVENT REPORTING, the fax numbers for SAE reporting in the US and Canada:

Serious adverse event reporting (24h)	
• **Fax**	**Europe and Rest of the World:** +32 2 386 24 21 **USA:** +1 800 880 6949 **Canada:** +1 877 582 8842
• **E-mail**	**Global:** DSICT@ucb.com

Have been changed to:

Serious adverse event reporting (24h)	
• **Fax**	**Europe and Rest of the World:** +32 2 386 24 21 **USA and Canada:** +1 800 880 6949 or +1 866 890 3175
• **E-mail**	**Global:** DSICT@ucb.com

Change #2

Section 2 INTRODUCTION, second paragraph, the second sentence:

Juvenile idiopathic arthritis is the most commonly diagnosed rheumatic disease affecting children less than 16 years of age with a prevalence of approximately 100 in 100,000.

Has been changed to:

Juvenile idiopathic arthritis is the most commonly diagnosed rheumatic disease affecting children less than 16 years of age with a prevalence of approximately 100 in 100,000 (Zitelli et al, 2012).

Change #3

Section 5.2 Schedule of study assessments, Table 5-1, entries for "TB screening and chest x-ray" and "TB questionnaire" and the associated footnotes "i" and "n" have been updated (new information in *italics* and **bold**):

Table 5-1 Schedule of study assessments

Study period	**Screening**	**Baseline**						
Week	**-4 to 0[a]**	**0**	**…**	**4, 8, 12, 16, (17[u]), 20, 24**	**32 and every 8 weeks thereafter**	**…**	**Early Disc/ End of Treatment**	**Final Visit[c]**
Visit (+/-3 days)[a]	**1**	**2**		**5 to 10**	**11 onwards**			**FV**
…								
TB screening[n] and chest x-ray[o]	X				***X[n]***			
TB questionnaire	X	X		X[i]	X[i]		X[i]	
…								

[i] TB questionnaire to be completed at Weeks 12 and 24, every 16 weeks thereafter, and Early Discontinuation/End of Treatment. If the Investigator suspects reactivation of ***latent*** TB or active TB, TB testing and/or a chest x-ray should be performed ***as outlined in Section 10.7.9.1***.

[n] TB screening if not performed within 3 months of Screening: Interferon-gamma release assay (IGRA) testing (QuantiFERON®) is required to be performed by the central lab for all study participants from 5 to 17 years of age. PPD testing is mandatory for study participants from 2 to 4 years of age in this study unless written documentation of BCG vaccination is available (refer to Section 6.2 [exclusion criterion 11] and Section 10.7.9). ***Following implementation of Protocol Amendment 7, IGRA testing (QuantiFERON) should be done once a year (approximately every 48 weeks) for all study participants from 5 to 17 years of age. For study participants from 2 to 4 years of age, both IGRA and PPD testing should be performed once a year (approximately every 48 weeks). In cases where written documentation of BCG vaccination is available or previous PPD test was positive, only IGRA should be performed (Section 10.7.9.2).***

Change #4

Section 7.8.2 Rescue medication, the first paragraph:

Rescue medication use is defined as any initiation of treatment or increase in dose of a medication used to treat JIA (in addition to the IMP) that is considered to impact the efficacy analyses. A study participant requiring rescue medication after first administration of IMP is considered as a treatment failure from that time point forward for the purpose of efficacy analyses.

Has been changed to:

Rescue medication use is defined as any initiation of treatment or increase in dose of a medication used to treat JIA (in addition to the IMP) that is considered to impact the efficacy analyses. A study participant requiring rescue medication after first administration of IMP is considered as a treatment failure from that time point forward for the purpose of efficacy analyses. Exception: A study participant initiating rescue medication use after the Week 56 visit will not be considered a treatment failure and the efficacy data will be analyzed as observed without imputation.

Change #5

Section 8.5 Visits 11 and continuing (Week 32 and every 8 weeks thereafter), a new bullet has been added as sixth bullet:

- TB screening once a year (approximately every 48 weeks)

Change #6

Section 10.1 Adverse events, the following section has been added:

10.1.7 Suspected transmission of an infectious agent via a medicinal product

For the purposes of reporting, any suspected transmission of an infectious agent via the study medication should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the CRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Change #7

Section 10.6 Laboratory measurements, a new paragraph has been added as 12th paragraph:

During the study and upon implementation of Protocol Amendment 7, IGRA testing should be done once a year (approximately every 48 weeks) for all study participants from 5 to 17 years of age. For study participants from 2 to 4 years of age, both IGRA and PPD testing should be performed once a year (approximately every 48 weeks). In cases where written documentation of BCG vaccination is available or previous PPD test was positive, only IGRA should be performed (Section 10.7.9.2).

Change #8

Section 10.6 Laboratory measurements, Table 10-2 Laboratory measurements, the entry “TB screening” and the associated footnote “d”:

TB screening[(d)]: IGRA (ages 5-17 years), PPD (ages 2-4 years)

[d] IGRA testing is required at Screening for all study participants aged 5 to 17 years; PPD testing is required for all study participants aged 2 to 4 years (except for study participants with documented BCG vaccination).

Have been changed to:

TB screening[(d)]: IGRA, PPD

[d] For TB testing refer to Section 10.7.9. IGRA is performed by the central lab.

Change #9

Section 10.7.9.1.1, the section heading:

10.7.9.1.1 Latent tuberculosis infection

Has been changed to:

10.7.9.1.1 Latent TB infection at study entry

Change #10

Section 10.7.9.1.1 Latent TB infection at study entry, second paragraph, the first and second sentences:

At Screening, study participants who have recently (defined as no more than 12 months prior to Screening) completed a full course of prophylaxis for LTB infection may be considered for study participation. Study participants who have received prophylactic therapy for LTB infection for at least 4 weeks prior to initiation or continuation of CZP treatment and who are committed to completing the full course of therapy, may be considered for study participation or can continue on the study.

Have been changed to:

At Screening, study participants who have recently (defined as no more than 12 months prior to Screening) completed a full course of prophylaxis for LTB infection may be considered for study participation. Study participants who have received prophylactic therapy for LTB infection for at least 4 weeks prior to initiation of CZP treatment and who are committed to completing the full course of therapy, may be considered for study participation.

Change #11

LTB infection and active TB identified during study, the heading and last sentence of the first paragraph:

In case a TB specialist excludes an active TB the study participant can proceed with the study medication no earlier than 4 weeks after the start of an appropriate prophylactic therapy.

Have been changed to:

Section 10.7.9.1.2 Latent TB infection and active TB identified during study

In case a TB specialist excludes an active TB the study participant can proceed with the study medication no earlier than 8 weeks after the start of an appropriate prophylactic therapy.

Change #12

Section 10.7.9.1.2 Latent TB infection and active TB identified during study, the second paragraph:

Any presumptive diagnosis or diagnosis of a TB infection is a reportable event, and confirmed active TB has to be reported as an SAE (please see Section 10.2.2 Procedures for reporting SAEs for details). The Investigator is to complete and submit the TB follow-up form provided.

Has been changed to:

Any confirmed diagnosis of a latent or active TB infection is a reportable event. Both cases have to be reported as AE of Interest and must be captured on an SAE report form (please tick the appropriate AE of Interest and/or SAE field(s) on the form to clearly indicate level of seriousness) and provided to the Sponsor in accordance with SAE reporting requirements (see Section 10.2.2 Procedures for reporting SAEs for details).

Change #13

Section 10.7.9.2 TB screening and testing, a new subsection has been added; subsequent subsections (for chest x-ray, IGRA test, and PPD skin test) have been renumbered:

10.7.9.2.1 Tuberculosis testing during the study for study participants above and below 5 years of age

Immediately following the implementation of Protocol Amendment 7 and upon signing the updated Informed Consent form, all study participants need to undergo TB testing as described below, unless available from the last 12 months.

In the case of a study participant who has previously had a positive IGRA test result and has completed prophylactic treatment in the past again tests positive in the IGRA testing, the study participant must be referred to a TB specialist for further assessment. The IGRA test might be repeated within 6 months in order to decide whether TB prophylactic treatment needs to be repeated. The PPD skin test should not be repeated in case of a previous positive result. The TB specialist, Study Physician, and Medical Monitor are requested to provide written approval for the study participant to continue being exposed to the study drug.

Study participants above 5 years of age

During the conduct of the study, the TB assessment by IGRA should be repeated once a year (approximately every 48 weeks). The test results will be reported as positive, negative, or indeterminate. Positive or indeterminate results must be reviewed by an experienced TB specialist, radiologist, or a pulmonologist. If the assessment by IGRA is positive or indeterminate on retest for study participants who were previously negative at Screening and not treated for LTB infection, the study participant may not continue study treatment without further evaluation by a TB specialist, prophylactic TB treatment, and discussion with the Medical Monitor, if LTB infection is identified.

If active TB is identified, the study participant must undergo appropriate study-specified withdrawal procedures.

Study participants below 5 years of age

During the conduct of the study, the TB assessment by both PPD skin test and IGRA should be repeated once a year (approximately every 48 weeks). If both tests are negative the study participant may continue in the study. The study participant should immediately discontinue study medication intake if 1 or both tests are positive and the study participant should be referred to a TB specialist. Should evaluation of the study participant by the appropriate TB specialist result in a diagnosis of LTB infection, the study medication must be withheld until the appropriate prophylactic therapy has been received for at least 8 weeks and the study participant is deemed likely to continue therapy to completion. The TB treatment must be discussed with the Medical Monitor, before study medication is restarted.

If active TB is identified, the study participant must undergo appropriate study-specified withdrawal procedures.

In countries with high BCG vaccination or previous high PPD skin test positivity, it might not be recommended to do or repeat the PPD skin test. The PPD skin test might be positive due to BCG vaccination; however, if the PPD skin test is not performed or positive in a pediatric study participants <5 years of age, it will not be allowed that the study participant continues in the study without written approval from a physician with expertise in pediatric TB.

Change #14

Section 10.7.9.2.2 Chest x-ray, the following paragraph has been added at the end of the section:

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

Change #15

Section 10.7.9.2.3 Interferon-gamma release assay (IGRA test):

The IGRA (QuantiFERON®-TB GOLD In-Tube test) is the protocol-required method of screening for TB in study participants from 5 to 17 years of age and will be performed at the central laboratory. The IGRA and PPD skin test may not be performed at the same time and a positive or indeterminate outcome in 1 test may not be overruled by a negative result in the other. If the result of the IGRA test is indeterminate, the test may be repeated once. If positive or indeterminate on retest, the study participant may not be enrolled without further evaluation and treatment, as well as discussion by the Investigator with the Study Physician or Medical Monitor. The retest must be done during the protocol-defined Screening window.

Has been changed to:

The IGRA (QuantiFERON®-TB GOLD In-Tube test) is the protocol-required method of screening for TB and will be performed at the central laboratory. If the result of the IGRA test is indeterminate, the test may be repeated once. If positive or indeterminate on retest, the study participant may not be enrolled without further evaluation and treatment, as well as discussion by the Investigator with the Study Physician or Medical Monitor. The retest must be done during the protocol-defined Screening window. During the study, TB screening with

IGRA will be repeated once yearly, ie, approximately every 48 weeks (after implementation of Protocol Amendment 7).

Change #16

Section 10.7.9.2.4 Tuberculin Purified Protein Derivative (PPD skin test):

In study participants from 2 to 4 years of age (except for study participants 2 to 4 years of age with a written documentation of BCG vaccination), the PPD skin test must be administered during Screening or within the 3 months prior to Screening in accordance with the instructions below.

Has been changed to:

In study participants from 2 to 4 years of age (except for study participants 2 to 4 years of age with a written documentation of BCG vaccination), the PPD skin test must be administered during Screening or within the 3 months prior to Screening and once yearly during the study, ie, approximately every 48 weeks (after implementation of Protocol Amendment 7) in accordance with the instructions below.

Change #17

Section 10.7.9.3 TB questionnaire (evaluation of signs and symptoms associated with TB and guidelines for evaluating exposure risk), second paragraph, the last 2 sentences:

Any presumptive diagnosis or diagnosis of LTB infection or active TB is a reportable event; refer to Section 10.2.2 for details. The Investigator is to complete and submit the TB follow-up form provided.

Have been changed to:

Any confirmed diagnosis of a latent or active TB infection is a reportable event; refer to Section 10.2.2 for details).

Change #18

Section 13.6 Handling of dropouts or missing data, the first 3 paragraphs:

For all binary efficacy endpoints assessing response, study participants who withdraw early will be considered as non-responders from that time point onwards.

For continuous efficacy endpoints, missing assessments will be imputed using the last observation carried forward (LOCF) approach. These summaries will be supported by observed case (OC) analyses.

Data collected after the taking of rescue medication will be treated as missing for continuous efficacy endpoints and non-response for binary efficacy endpoints in all analyses except where specifically stated otherwise. See Section 7.8.2 for a list of medications which would result in data at only the next scheduled visit (and not all subsequent visits) being treated as missing/non-response. These data will then be imputed as for any other missing data.

Have been changed to:

For all binary efficacy endpoints assessing response, study participants who withdraw early will be considered as non-responders from that time point onwards. The exception is efficacy data for study participants who withdraw after Week 56: Per Protocol Amendment 7, these will not be imputed (as nonresponse or missing) and will be analyzed as observed.

For continuous efficacy endpoints, missing assessments will be imputed using the last observation carried forward (LOCF) approach. These summaries will be supported by observed case (OC) analyses. Per Protocol Amendment 7, missing assessments after Week 56 will no longer be imputed and will be analyzed as observed.

Data collected after the taking of rescue medication will be treated as missing for continuous efficacy endpoints and non-response for binary efficacy endpoints in all analyses except where specifically stated otherwise. See Section 7.8.2 for a list of medications which would result in data at only the next scheduled visit (and not all subsequent visits) being treated as missing/non-response. These data will then be imputed as for any other missing data. The exception is any rescue medication use that is initiated after Week 56: Per Protocol Amendment 7, efficacy data after any rescue medication use initiated after Week 56 will not be imputed (as nonresponse or missing) and will be analyzed as observed.

Change #19

Section 16 REFERENCES, the following publication has been added:

Zitelli B, McIntire S, Nowalk A. Zitelli and Davis' Atlas of pediatric physical diagnosis, 6th edition. Chapter 7: Rheumatology, Section: Juvenile Idiopathic Arthritis. Elsevier Health Sciences, 2012, 264.

17.18 Protocol Amendment 8

Rationale for the amendment

The primary purpose of this substantial amendment is to reduce the study participants' burden by limiting the frequency of on-site visits, safety sampling, and efficacy assessments.

The frequency of on-site visits will be reduced from every 8 weeks to every 16 weeks in this long-term study. At the time of implementing Protocol Amendment 8, all ongoing study participants have at least completed the visit for Week 180. As before, on-site CZP administration between scheduled visits is offered as needed.

The frequency of safety sampling (blood sampling and urinalysis) will be extended from every 8 weeks to every 16 weeks to reduce study participants' burden in line with the updated on-site CZP administration schedule. Safety data collected previously during the study and close evaluation by the DSMB support the extension of sampling frequency.

This longer interval will also be implemented for efficacy assessments to further reduce the study participants' burden and will be appropriate to describe the long-term efficacy of CZP.

In addition, blood samples to determine CZP plasma concentrations and anti-CZP antibodies will no longer be collected in the study to further reduce study participants' burden. Pharmacokinetic data from this study (assayed with an ELISA technique) will not be used for submission to the FDA to complete the Pediatric Research Equity Act commitment, primarily due to some deficiencies detected on the bioanalytical assay used. UCB determined that further collection of additional samples to determine CZP plasma concentrations and anti-CZP antibodies would be of limited utility and an undue burden on the study participants. There is also limited value in collecting anti-CZP antibody and CZP plasma concentration data after >4 years of CZP exposure. Discontinuation of blood sample collection for further characterization of CZP PK and immunogenicity is supported by the DSMB as the PK and immunogenicity data available to date is considered sufficient from a safety perspective and for PK characterization.

For the final analysis at the end of the study, UCB will reanalyze all the available samples with sufficient volume with a new MSD bioanalytical assay that is fully validated and that meets current regulatory standards. This re-assayed PK data will be used for final study reporting and thus will not be compared to the previously reported RA adult concentrations, as a different bioanalytical technique was used.

Also, minor editorial changes have been made to correct typographical errors and to update abbreviations.

Modifications and changes

Global changes

The following changes have been made throughout the protocol:

- Study contact details have been updated.

- Safety laboratory assessments (including urinalysis), efficacy assessments, and on-site CZP administration frequency has been changed from every 8 weeks to every 16 weeks.
- Cessation of samples for CZP plasma concentration and anti-CZP antibodies has been implemented.
- Updated PK analysis section as the previous ELISA technique will no longer be used and the samples need to be re-assayed using a new MSD assay.
- Reference to Week 56 interim analysis removed as this interim analysis is no longer necessary following the [redacted].
- Tanner stage assessment frequency has been updated from every 24 weeks to every 48 weeks, and only for study participants that have not reached Tanner stage V.

Specific changes

This section displays the modifications in this amendment compared with the previous version of the protocol dated 22 Sep 2016. The changes are displayed in the order of appearance.

Change #1

STUDY CONTACT INFORMATION, contact details of the Clinical Project Manager:

Clinical Project Manager

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

Has been changed to:

Clinical Project Manager

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

Change #2

STUDY CONTACT INFORMATION, contact details of the Clinical Trial Biostatistician:

Clinical Trial Biostatistician

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

Has been changed to:

Clinical Trial Biostatistician

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

Change #3

SERIOUS ADVERSE EVENT REPORTING, global email:

Serious adverse event reporting (24h)	
• **Fax**	**Europe and Rest of the World:** +32 2 386 24 21 **USA and Canada:** +1 800 880 6949 or +1 866 890 3175
• **E-mail**	**Global:** DSICT@ucb.com

Has been changed to:

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **USA and Canada:** +1 800 880 6949 or +1 866 890 3175
E-mail	**Global:** DS_ICT@ucb.com

Change #4

Section 1, Summary, seventh paragraph

Full interim analyses will be performed after all active study participants have completed the Week 24 (Visit 10) assessments, as well as after all active study participants have completed the Week 56 (Visit 14) assessments. The study will continue until the approval of the marketing application for the polyarticular-course JIA indication in the study participant's country or region, or until discontinuation of the study based on the Week 16 analysis of response, or until further notice from UCB.

Has been changed to:

A full interim analysis will be performed after all active study participants have completed the Week 24 (Visit 10) assessments. The study will continue until the approval of the marketing application for the polyarticular-course JIA indication in the study participant's country or region, or until discontinuation of the study based on the Week 16 analysis of response, or until further notice from UCB.

Change #5

Section 1, Summary, eighth paragraph

Certolizumab pegol will be administered as a fixed dose based on weight throughout the study consisting of 3 loading doses at Weeks 0, 2, and 4 (minimum=50mg every 2 weeks [Q2W], maximum=200mg Q2W) followed by a maintenance dose (minimum=50mg every 4 weeks [Q4W], maximum=100mg Q2W). Prior to implementation of Protocol Amendments 4 and 5, the minimum and maximum loading doses in the study were CZP 100mg Q2W and CZP 400mg Q2W, respectively, and the minimum and maximum maintenance doses were CZP 50mg Q2W and CZP 200mg Q2W, respectively. Interim analysis of PK data will compare plasma concentration data from this study with CZP plasma concentrations observed previously in adult study participants with rheumatoid arthritis (RA). This CZP plasma concentration analysis will be done on an ongoing basis throughout the study, starting when 6 study participants in 1 of the age groups have completed Week 12 (Visit 7). Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future analyses indicate that plasma concentrations of JIA study participants are outside of the exposure range observed in previous adult RA studies, the dosing algorithm may be changed via a protocol amendment.

Has been changed to:

Certolizumab pegol will be administered as a fixed dose based on weight throughout the study consisting of 3 loading doses at Weeks 0, 2, and 4 (minimum=50mg every 2 weeks [Q2W], maximum=200mg Q2W) followed by a maintenance dose (minimum=50mg every 4 weeks [Q4W], maximum=100mg Q2W). Prior to implementation of Protocol Amendments 4 and 5, the minimum and maximum loading doses in the study were CZP 100mg Q2W and CZP 400mg Q2W, respectively, and the minimum and maximum

maintenance doses were CZP 50mg Q2W and CZP 200mg Q2W, respectively. Interim analysis of PK data will compare plasma concentration data from this study with CZP plasma concentrations observed previously in adult study participants with rheumatoid arthritis (RA). Interim analysis of CZP plasma concentrations was started when 6 study participants in 1 of the age groups completed Week 12 (Visit 7). Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future analyses indicate that plasma concentrations of JIA study participants are outside of the exposure range observed in previous adult RA studies, the dosing algorithm may be changed via a protocol amendment.

Change #6

Section 4.3, Other variables, other safety variables, bullet 3

- Assessments of study participants' developmental stages and growth (height, weight) will be performed to determine Tanner stages at Baseline, every 24 weeks thereafter, and the Early Discontinuation/End of Treatment Visit (weight at every visit through Final Visit).

Has been changed to:

- Assessments of study participants' developmental stages and growth (height, weight) will be performed to determine Tanner stages at Baseline, every 24 weeks thereafter, and the Early Discontinuation/End of Treatment Visit (weight at every visit through Final Visit). Following Protocol Amendment 8, Tanner stages assessment will be performed every 48 weeks, and only for those study participants who have not reached Tanner stage V.

Change #7

Section 4.3, Other variables, other efficacy and health outcomes variables, bullets 15 and 16; and Section 13.5 Planned efficacy and health outcomes analyses, bullets 16 and 17

- Change from Baseline in FPS-R (child-reported, ages 5 to 11 years), daily during the first week of treatment; Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit.
- Change from Baseline in JIA Pain VAS, daily during the first 7 days of the study (acute and standard versions); and at Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit (standard version) for study participants ages 12 to 17 years.

Have been changed to:

- Change from Baseline in FPS-R (child-reported, ages 5 to 11 years), daily during the first week of treatment; Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit. Following Protocol Amendment 8, change from Baseline on FPS-R is assessed every 16 weeks.

- Change from Baseline in JIA Pain VAS, daily during the first 7 days of the study (acute and standard versions); and at Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit (standard version) for study participants ages 12 to 17 years. Following Protocol Amendment 8, change from Baseline in JIA Pain VAS is assessed every 16 weeks.

Change #8

Section 5.1, Study description, fifth paragraph

Full interim analyses will be performed:

- After all active study participants have completed the Week 24 (Visit 10) assessments
- After all active study participants have completed the Week 56 (Visit 14) assessments

Has been changed to:

A full interim analysis will be performed after all active study participants have completed the Week 24 (Visit 10) assessments.

Change #9

Section 5.1, Study description, eighth paragraph

Interim analysis of PK data will compare CZP plasma concentration data from this study with plasma concentrations observed previously in adult study participants with RA. This CZP plasma concentration analysis will be done on an ongoing basis throughout the study, starting when 6 study participants in 1 of the age groups have completed Week 12 (Visit 7).

Has been changed to:

Interim analysis of PK data will compare CZP plasma concentration data from this study with plasma concentrations observed previously in adult study participants with RA. Interim analysis of CZP plasma concentrations was started when 6 study participants in 1 of the age groups completed Week 12 (Visit 7).

Change #10

Section 5.1, Study description

The following text was added:

Pharmacokinetic data from this study (assayed with an enzyme-linked immunosorbent assay [ELISA] technique) will not be used for submission to the Food and Drug Administration (FDA) to complete the Pediatric Research Equity Act commitment, primarily due to some deficiencies detected on the bioanalytical assay used. UCB determined that further collection of additional samples to determine CZP plasma concentrations and anti-CZP antibodies

would be of limited utility and an undue burden on the study participants. Following Protocol Amendment 8, these samples will no longer be collected.

For the final analysis at the end of the study, UCB will reanalyze all the available samples with sufficient volume with a new Meso Scale Discovery (MSD) bioanalytical assay that is fully validated and that meets current regulatory standards. This PK data, from the re-assayed samples, will be used for final study reporting and thus will not be compared to the previously reported RA adult concentrations, as a different bioanalytical technique was used.

Change #11

Section 5.2, Schedule of study assessments, Table 5-1, CZP plasma concentrations and anti-CZP antibodies row

Study period		
Week	**Early Disc/ End of Treatment**	**Final Visit[(c)]**
Visit (+/-3 days)[(a)]		**FV**
…		
CZP plasma concentrations and anti-CZP antibodies	X	X
…		

Has been changed to:

Study period		
Week	**Early Disc/ End of Treatment**	**Final Visit[(c)]**
Visit (+/-3 days)[(a)]		**FV**
…		
CZP plasma concentrations and anti-CZP antibodies		
…		

Change #12

Section 5.2, Schedule of study assessments, Table 5-1, footnotes f, q, r, and v

[f] Height and Tanner stages to be measured at Weeks 24 and 48, every 24 weeks thereafter and at Early Discontinuation/End of Treatment.

[q] For study participants ages 5 to 11 years. Daily assessment during the first week (Baseline and Day 1 to Day 7, to be collected at Week 1). In addition, to be completed at Weeks 4, 12, 16, 24, and then every 8 weeks thereafter through the End of Treatment/Early Discontinuation Visit.

[r] For study participants ages 12 to 17 years. Daily assessment of acute VAS version during the first week (at Baseline and Day 1 to Day 7, to be collected at Week 1). In addition, standard VAS version to be completed at Baseline, Weeks 4, 12, 16, 24, and then every 8 weeks thereafter through the End of Treatment/Early Discontinuation Visit for study participants ages 12 to 17 years.

[v] CZP plasma concentration and anti-CZP antibodies to be measured at Weeks 32, 40, and 48 and every 24 weeks thereafter. For study participants already enrolled and treated prior to the implementation of Protocol Amendment 4 and hence undergoing a reduction of their dose, additional PK samples will be collected prior to

dosing at the visit the dose change occurs and at the next 3 site visits following the dose change, ie, additional PK samples will be collected at the Unscheduled Visits or at the regular visits if not already planned per regular schedule. Afterwards, the regular PK sampling schedule applies.

Have been changed to:

[f] Height and Tanner stages to be measured at Weeks 24 and 48, every 24 weeks thereafter (Tanner stages will be measured every 48 weeks and only for study participants who have not reached Tanner stage V following Protocol Amendment 8) and at Early Discontinuation/End of Treatment.

[q] For study participants ages 5 to 11 years. Daily assessment during the first week (Baseline and Day 1 to Day 7, to be collected at Week 1). In addition, to be completed at Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (every 16 weeks following Protocol Amendment 8) through the End of Treatment/Early Discontinuation Visit.

[r] For study participants ages 12 to 17 years. Daily assessment of acute VAS version during the first week (at Baseline and Day 1 to Day 7, to be collected at Week 1). In addition, standard VAS version to be completed at Baseline, Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (every 16 weeks following Protocol Amendment 8) through the End of Treatment/Early Discontinuation Visit for study participants ages 12 to 17 years.

[v] CZP plasma concentration and anti-CZP antibodies to be measured at Weeks 32, 40, and 48 and every 24 weeks thereafter. For study participants already enrolled and treated prior to the implementation of Protocol Amendment 4 and hence undergoing a reduction of their dose, additional PK samples will be collected prior to dosing at the visit the dose change occurs and at the next 3 site visits following the dose change, ie, additional PK samples will be collected at the Unscheduled Visits or at the regular visits if not already planned per regular schedule. Afterwards, the regular PK sampling schedule applies. Following Protocol Amendment 8, samples for CZP plasma concentration and anti-CZP antibodies will no longer be collected.

Change #13

Section 5.2, Schedule of study assessments, Table 5-1, footnote z was added:

[z] Following Protocol Amendment 8, on-site CZP administration, safety sampling, and efficacy assessment frequency changes to every 16 weeks instead of every 8 weeks, if administration at home is feasible. The option to come to the site for CZP administration between scheduled visits is available as needed.

Change #14

Section 5.3, Schematic diagram, footnote a was added:

[a] Following Protocol Amendment 8, visits will be every 16 weeks instead of every 8 weeks.

Change #15

Section 8.5, section heading

Visits 11 and continuing (Week 32 and every 8 weeks thereafter)

Has been changed to:

Visits 11 and continuing (Week 32 and every 8 weeks thereafter [every 16 weeks following Protocol Amendment 8])

Change #16

Section 8.5, Visits 11 and continuing, bullets 2, 4, and 28

- Height (Week 48 and every 24 weeks thereafter)
- Tanner stages (except growth; Week 48 and every 24 weeks thereafter)
- CZP plasma concentrations and anti-CZP antibodies (Weeks 32, 40, and 48 and every 24 weeks thereafter, OR if a dose change is performed at the current visit OR if the study participant's dose was changed during 1 of the last 3 visits following Protocol Amendment 4)

Have been changed to:

- Height (Week 48 and every 24 weeks thereafter [every 48 weeks following Protocol Amendment 8])
- Tanner stages (except growth; Week 48 and every 24 weeks thereafter [every 48 weeks, and only for study participants who have not reached Tanner stage V following Protocol Amendment 8])
- CZP plasma concentrations and anti-CZP antibodies (Weeks 32, 40, and 48 and every 24 weeks thereafter, OR if a dose change is performed at the current visit OR if the study participant's dose was changed during 1 of the last 3 visits following Protocol Amendment 4; following Protocol Amendment 8, these samples will no longer be collected)

Change #17

Section 8.7, Early Discontinuation/End of Treatment Visit, second to last bullet

- CZP plasma concentrations and anti-CZP antibodies

Has been changed to:

- CZP plasma concentrations and anti-CZP antibodies (following Protocol Amendment 8, these samples will no longer be collected)

Change #18

Section 8.8, Final Visit, last bullet

- CZP plasma concentrations and anti-CZP antibodies

Has been changed to:

- CZP plasma concentrations and anti-CZP antibodies (following Protocol Amendment 8, these samples will no longer be collected)

Change #19

Section 9, Assessment of Pharmacokinetics and Immunological Variables

The following text was added:

Following Protocol Amendment 8, blood samples for determination of CZP plasma concentrations and anti-CZP antibodies will not be collected throughout the remainder of the study.

Change #20

Section 10.6, Laboratory measurements, first paragraph

Hematology, biochemistry, and urinalysis samples will be collected at Screening, Baseline, Weeks 4, 8, 12, 16, 20, 24, 32, every 8 weeks thereafter, the Early Discontinuation/End of Treatment Visit, and the Final Visit 12 weeks after the last dose of study medication. At Week 1, only CRP and PK samples will be collected and at Week 2, only CRP samples will be collected. In addition, hematology, biochemistry, and CRP samples will be collected at Unscheduled Visits related to the dose change implemented with Protocol Amendment 4.

Has been changed to:

Hematology, biochemistry, and urinalysis samples will be collected at Screening, Baseline, Weeks 4, 8, 12, 16, 20, 24, 32, every 8 weeks thereafter (every 16 weeks following Protocol Amendment 8), the Early Discontinuation/End of Treatment Visit, and the Final Visit 12 weeks after the last dose of study medication. At Week 1, only CRP and PK samples will be collected and at Week 2, only CRP samples will be collected. In addition, hematology, biochemistry, and CRP samples will be collected at Unscheduled Visits related to the dose change implemented with Protocol Amendment 4.

Change #21

Section 10.7.2, Growth (height and weight), first paragraph

Height will be recorded at Screening, Baseline, every 24 weeks thereafter, and the Early Discontinuation/End of Treatment Visit. Height will be recorded after the shoes have been removed. Height should preferably be measured with a wall-mounted stadiometer.

Has been changed to:

Height will be recorded at Screening, Baseline, every 24 weeks thereafter (every 48 weeks following Protocol Amendment 8), and the Early Discontinuation/End of Treatment Visit. Height will be recorded after the shoes have been removed. Height should preferably be measured with a wall-mounted stadiometer.

Change #22

Section 10.7.3, Tanner stages

Assessments of study participants' developmental stages on external genitalia and pubic hair (boys) and on breast and pubic hair (girls) will be performed to determine Tanner stages (Marshall and Tanner, 1969; Marshall and Tanner, 1970). These assessments will be performed at Baseline, every 24 weeks thereafter, and the Early Discontinuation/End of Treatment Visit.

Has been changed to:

Assessments of study participants' developmental stages on external genitalia and pubic hair (boys) and on breast and pubic hair (girls) will be performed to determine Tanner stages (Marshall and Tanner, 1969; Marshall and Tanner, 1970). These assessments will be performed at Baseline, every 24 weeks thereafter, and the Early Discontinuation/End of Treatment Visit. Following Protocol Amendment 8, the assessments will be performed every 48 weeks, and only for study participants who have not reached Tanner stage V.

Change #23

Section 11.12, Faces Pain Scale-Revised (FPS-R), second paragraph

The FPS-R is provided in Appendix 17.4. The FPS-R will be administered at Baseline and then daily during the first week of the study; at Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit. The questionnaire should be checked by site personnel for completeness.

Has been changed to:

The FPS-R is provided in Appendix 17.4. The FPS-R will be administered at Baseline and then daily during the first week of the study; at Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter (every 16 weeks following Protocol Amendment 8) through the Early Discontinuation/End of Treatment Visit. The questionnaire should be checked by site personnel for completeness.

Change #24

Section 11.13, Patient's Assessment of Arthritis Pain (JIA Pain VAS), second paragraph

Both versions of the JIA Pain VAS are provided in Appendix 17.5 and Appendix 17.6. The Pain (VAS) will be completed at Baseline (acute and standard versions), daily during the first week of treatment (acute version); Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit (standard version). The scale should be checked by site personnel for completeness.

Has been changed to:

Both versions of the JIA Pain VAS are provided in Appendix 17.5 and Appendix 17.6. The Pain (VAS) will be completed at Baseline (acute and standard versions), daily during the first week of treatment (acute version); Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter (every 16 weeks following Protocol Amendment 8) through the Early

Discontinuation/End of Treatment Visit (standard version). The scale should be checked by site personnel for completeness.

Change #25

Section 11.14, Fatigue Assessment Scale (NRS), fourth paragraph

The Fatigue Assessment Scale is provided in Appendix 17.7. The Fatigue Assessment Scale will be assessed at Baseline, Weeks 1, 2, 4, 8, then every 8 weeks thereafter, and the Early Discontinuation/End of Treatment Visit. Preferably, the same parent/caregiver should complete the scale for each visit. The scale will not be completed if the study participant is not living with a parent/caregiver at least part-time, ie, the parent/caregiver is not able to answer the question appropriately. The scale should be checked by site personnel for completeness.

Has been changed to:

The Fatigue Assessment Scale is provided in Appendix 17.7. The Fatigue Assessment Scale will be assessed at Baseline, Weeks 1, 2, 4, 8, 16, 24, 32, then every 8 weeks thereafter (every 16 weeks following Protocol Amendment 8), and the Early Discontinuation/End of Treatment Visit. Preferably, the same parent/caregiver should complete the scale for each visit. The scale will not be completed if the study participant is not living with a parent/caregiver at least part-time, ie, the parent/caregiver is not able to answer the question appropriately. The scale should be checked by site personnel for completeness.

Change #26

Section 13.4, Planned PK, PD, and immunological variable analysis, second, third, and fourth paragraphs

Plasma concentrations will be used to build a PopPK model using either a Bayesian approach with the Winbugs software or meta-analysis with the nonlinear mixed-effect modeling (NONMEM) software.

In the Bayesian approach, the distributions of PK parameters estimated from adult data (from the PopPK analysis in C87068 and CL0153) will be incorporated as prior information in the model to estimate pediatric PK parameters. This combination of prior knowledge and sparse pediatric data will be analyzed within Winbugs.

The meta-analysis will be performed by adding the pediatric data to the adult data that were previously used to perform the adult PopPK analysis within NONMEM (C87068 and CL0153).

Have been changed to:

Plasma concentrations will be used to build a PopPK model with the nonlinear mixed-effect modeling (NONMEM) software.

A meta-analysis was previously performed by adding the pediatric data to the adult data in a PopPK analysis within NONMEM (C87068 and CL0153) for the Week 24 interim analysis (with ELISA data).

Change #27

Section 13.4, Planned PK, PD, and immunological variable analysis

The following text was added:

For the final analysis, UCB will be re-assaying all available PK samples (ie, for which sufficient volume is available) with a newly developed MSD bioanalytical assay. The data from the re-assayed RA0043 PK samples will be used to build a PopPK model.

Change #28

Section 13.5, Planned efficacy and health outcomes analyses, bullets 16 and 17

- Change from Baseline on FPS-R (child-reported, for study participants ages 5 to 11 years), daily during the first 7 days of treatment; Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit.
- Change from Baseline in JIA Pain VAS, daily during the first week of the study (acute and standard versions); Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit (standard version) for study participants ages 12 to 17 years.

Have been changed to:

- Change from Baseline on FPS-R (child-reported, for study participants ages 5 to 11 years), daily during the first 7 days of treatment; Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit. Following Protocol Amendment 8, change from Baseline on FPS-R is assessed every 16 weeks.
- Change from Baseline in JIA Pain VAS, daily during the first week of the study (acute and standard versions); Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit (standard version) for study participants ages 12 to 17 years. Following Protocol Amendment 8, change from Baseline in JIA Pain VAS is assessed every 16 weeks.

Change #29

Section 13.7, Planned interim analysis and data monitoring, first paragraph

Interim analysis of PK data will compare CZP plasma concentration data from this study with CZP plasma concentrations observed previously in adult study participants with RA. This plasma concentration analysis will be done on an ongoing basis throughout the study, starting when 6 study participants in 1 of the age groups have completed Week 12 (Visit 7).

Has been changed to:

Interim analysis of PK data will compare CZP plasma concentration data from this study with CZP plasma concentrations observed previously in adult study participants with RA. Interim analysis of CZP plasma concentrations was started when 6 study participants in 1 of the age groups completed Week 12 (Visit 7).

Change #30

Section 13.7, Planned interim analysis and data monitoring, fifth paragraph

The CZP plasma concentrations will be monitored on an ongoing basis following the change in dose regimen to confirm they are within the targeted adult range.

Has been changed to:

For the Week 24 interim clinical study report, the CZP plasma concentrations were monitored following the change in dose regimen to confirm they were within the targeted adult range. Following Protocol Amendment 8, no more interim PK analyses will be performed, and the final PK data to be reported will use a new MSD assay, and consequently no further comparison will be performed with respect to the adult RA concentrations range.

Change #31

Section 13.7, Planned interim analysis and data monitoring, eighth paragraph

The following text was removed:

A second full interim analysis of all safety and efficacy endpoints will be performed based upon 56 weeks of exposure (Visit 14).

17.19 Protocol Amendment 9

Rationale for the amendment

Protocol Amendment 9 is being undertaken in support of the pJIA PREA requirement for CZP. The primary purpose of this substantial amendment is to enroll an additional 30 study participants on the original CZP dose regimen in order to adequately assess the exposure levels and clinical experience of CZP in pJIA at both the reduced and original CZP dose regimens and also adequately support the safety assessment of the original CZP dosing regimen. More of the safety data collected in the study to date has been on the reduced dose, and which of these dose regimens to be included in the marketing application for CZP in pJIA is still to be determined.

Pharmacokinetic data from this study that were assayed with an ELISA technique will not be used for submission to the FDA to complete the PREA commitment, primarily due to deficiencies detected with the use of the bioanalytical assay within RA0043, which rendered the PK data for the PopPK analysis and simulations that informed the dose reduction in Protocol Amendment 4 and 5 unusable from a regulatory standpoint. An ECLIA method, for which selectivity had previously been assessed in the RA matrix, has now been validated to meet the standards set in the regulatory guidance for analytical procedures and methods validations for drugs and biologics. All study participants enrolled following Protocol Amendment 9 will have plasma concentrations of CZP and anti-CZP antibodies analyzed using the ECLIA method. In addition, PK and ADA samples (for which sufficient volume is available) collected in this study prior to Protocol Amendment 9 will be analyzed with the ECLIA method. The collective ECLIA-based PK data for this study will form the basis of any future CZP modeling and simulation work.

Additional updates were made to fix typographical errors and to reduce redundancy within the protocol.

Modifications and changes

Global changes

The following changes have been made throughout the protocol:

- ‘Subject’ was changed to ‘study participant’.
- Study contact details have been updated.
- Updated primary PK endpoints and primary safety endpoints to be more specific.
- An additional 30 study participants will be enrolled on the original dose regimen.
- Updated exclusion criteria to align with current clinical guidelines. The updated exclusion criteria are specific for the newly enrolled study participants and will not count as protocol deviations for study participants enrolled prior to Protocol Amendment 9.
- The rationale for study design and selection of dose section was restructured for clarity and to describe the rationale for adding the 30 study participants on the original CZP dose.

- Withdrawal criteria were updated to encourage study participants to remain in the study in the event of study medication discontinuation.
- Study participants on the reduced CZP dose regimen will be able to switch to the original CZP dose regimen at the discretion of the Investigator.
- Sampling for CZP plasma concentration and anti-CZP antibodies will occur for study participants enrolled following Protocol Amendment 9.
- Updated statistical considerations section to reflect that study participants on the reduced CZP dose can switch dose regimens to the original CZP dose.
- Updated safety analysis section to reflect updated primary safety endpoints of incidence of serious TEAEs and TEAEs leading to permanent withdrawal of IMP.
- Updated PK analysis section to reflect updated primary PK endpoints of CZP plasma concentrations and anti-CZP antibody levels at Week 16 and Week 48.
- Updated interim analysis section to reflect previous interim analyses and the analyses to be conducted with the newly enrolled study participants on the original CZP dose.
- Removed the Week 16 futility analysis and the Week 56 analysis
- Assessment and management of TB and TB risk factors has been updated to reflect current UCB guidelines.

Specific changes

This section displays the modifications in this amendment compared with the previous version of the protocol dated 24 Jun 2019. The changes are displayed in the order of appearance.

Change #1

STUDY CONTACT INFORMATION, contact details of the Sponsor Study Physician:

Sponsor Study Physician

Name:	[redacted]
Address:	Chemin du Foriest B - 1420 Braine-l'Alleud Belgium
Phone:	[redacted]
Fax:	

Has been changed to:

Sponsor Study Physician

Name:	[redacted]
Address:	UCB 208 Bath Road

	Slough SL1 3WE
Phone:	[redacted]
Fax:	

Change #2

STUDY CONTACT INFORMATION, contact details of the Clinical Trial Biostatistician:

Clinical Trial Biostatistician

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

Has been changed to:

Clinical Trial Biostatistician

Name:	[redacted]
Address:	UCB 208 Bath Road Slough SL1 3WE
Phone:	[redacted]
Fax:	N/A

Change #3

Section 1, paragraph 4 and 5:

Approximately 195 subjects will be screened to enroll 156 subjects in this study. The study consists of a Screening Period of up to 4 weeks; eligible subjects will then enter an open-label Treatment Period which will continue until the approval of the marketing application for the indication of polyarticular-course JIA in the subject's country or region or until further notice from UCB. A Final Visit will be conducted 12 weeks after last dose of study medication.

A minimum of 10 subjects will be enrolled on the reduced CZP dose regimen (Protocol Amendment 5) in each weight range of 10 to <20kg (22 to <44lb), 20 to <40kg (44 to <88lb), and ≥40kg (≥88lb). A minimum of 10 subjects will be enrolled in each age category of 2 to 5 years, 6 to 11 years, and 12 to 17 years, irrespective of the dose regimen. A minimum of 25 subjects will be enrolled who receive CZP as monotherapy (ie, subjects with established intolerability or inadequate response to MTX), irrespective of the dose regimen. A minimum

of 10 subjects with ERA will be enrolled, irrespective of the dose regimen. Each of these categories is assessed independently.

Has been changed to:

Approximately 195 study participants are planned to be screened to enroll 156 study participants in this study, as follows:

- A minimum of 10 study participants will be enrolled on the reduced CZP dose regimen (Protocol Amendment 5) in each weight range of 10 to <20kg (22 to <44lb), 20 to <40kg (44 to <88lb), and ≥40kg (≥88lb).
- A minimum of 10 study participants will be enrolled in each age category of 2 to 5 years, 6 to 11 years, and 12 to 17 years, irrespective of the dose regimen.
- A minimum of 25 study participants will be enrolled who receive CZP as monotherapy (ie, study participants with established intolerability or inadequate response to MTX), irrespective of the dose regimen.
- A minimum of 10 study participants with ERA will be enrolled, irrespective of the dose regimen.

Each of these categories is assessed independently. In order to further support the safety assessment of the original CZP dose, as more of the safety data collected in the study to date has been on the reduced dose, an additional 30 study participants will be enrolled on the original dose regimen with the aim to enroll at least 5 study participants in each weight range of 10 to <20kg (22 to <44lb), 20 to <40kg (44 to <88lb), and ≥40kg (≥88lb) following Protocol Amendment 9.

Change #4

Section 1, paragraph 6, was removed:

An interim analysis of the American College of Rheumatology Pediatric 30% (PedACR30) response rate will be performed after all active subjects have completed the Week 16 (Visit 8) assessments. The study will be discontinued if less than 50% of the study population enrolled on the reduced CZP dose regimen (Protocol Amendment 5) achieves a PedACR30 response at Week 16.

Change #5

Section 1, paragraph 7:

A full interim analysis will be performed after all active subjects have completed the Week 24 (Visit 10) assessments. The study will continue until the approval of the marketing application for the polyarticular-course JIA indication in the subject's country or region, or until discontinuation of the study based on the Week 16 analysis of response, or until further notice from UCB.

Has been changed to:

A full interim analysis will be performed after all active study participants have completed the Week 24 (Visit 10) assessments.

Change #6

Section 1, paragraph 8:

Certolizumab pegol will be administered as a fixed dose based on weight throughout the study consisting of 3 loading doses at Weeks 0, 2, and 4 (minimum=50mg every 2 weeks [Q2W], maximum=200mg Q2W) followed by a maintenance dose (minimum=50mg every 4 weeks [Q4W], maximum=100mg Q2W). Prior to implementation of Protocol Amendments 4 and 5, the minimum and maximum loading doses in the study were CZP 100mg Q2W and CZP 400mg Q2W, respectively, and the minimum and maximum maintenance doses were CZP 50mg Q2W and CZP 200mg Q2W, respectively. Interim analysis of PK data will compare plasma concentration data from this study with CZP plasma concentrations observed previously in adult subjects with rheumatoid arthritis (RA). Interim analysis of CZP plasma concentrations was started when 6 subjects in 1 of the age groups completed Week 12 (Visit 7). Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future analyses indicate that plasma concentrations of JIA subjects are outside of the exposure range observed in previous adult RA studies, the dosing algorithm may be changed via a protocol amendment.

Has been changed to:

Certolizumab pegol will be administered as a fixed dose based on weight throughout the study consisting of 3 loading doses at Weeks 0, 2, and 4, followed by maintenance doses Q2W. The original minimum and maximum loading doses in the study were CZP 100mg Q2W and CZP 400mg Q2W, respectively, and the original minimum and maximum maintenance doses were CZP 50mg Q2W and CZP 200mg Q2W, respectively. Based on an interim PopPK analysis of RA0043 data, the minimum and maximum loading doses in the study were adjusted to CZP 50mg Q2W and CZP 200mg Q2W, respectively, and the minimum and maximum maintenance doses were adjusted to CZP 50mg Q4W and CZP 100mg Q2W, respectively, following implementation of Protocol Amendments 4 and 5.

Change #7

Section 1, Summary

The following text was added:

However, it was later determined that there were deficiencies detected with the use of the bioanalytical assay within RA0043, which rendered the PK data for the PopPK analysis and simulations that informed the dose reduction in Protocol Amendment 4 and 5 unusable from a regulatory standpoint. Accordingly, PK samples were no longer collected for study participants on the reduced CZP dose regimen following implementation of Protocol Amendment 8.

An electrochemiluminescent immuno-assay (ECLIA) method, for which selectivity had previously been assessed in the RA matrix, has now been validated to meet the standards set in the regulatory guidance for analytical procedures and methods validations for drugs and biologics.

Based on 24-week interim results from the first 163 participants enrolled in RA0043, both the original and reduced dose regimens showed safety profiles similar to the approved CZP dose regimen in the adult RA population. The overall clinical response in this analysis (taking both dose regimens into account) was PedACR30 and PedACR50 responses of 77.3% and 67.5%, respectively at Week 12. The response from the original dose regimen was 75.6% for PedACR30 and 64.1% for PedACR50. PedACR50 response demonstrates a highly clinically relevant decrease in disease activity.

Therefore, in order to adequately assess the exposure levels and clinical experience of CZP in JIA at both the reduced and original CZP dose regimens and also adequately support the safety assessment of the original CZP dosing regimen, as more of the safety data collected in the study to date has been on the reduced dose, 30 additional study participants will be enrolled on the original CZP dose regimen following Protocol Amendment 9. All study participants enrolled following Protocol Amendment 9 will have plasma concentrations of CZP and anti-CZP antibodies analyzed using the ECLIA method. In addition, PK and ADA samples (for which sufficient volume is available) collected in this study prior to Protocol Amendment 9 will be analyzed with the ECLIA method. The collective ECLIA-based PK data for this study will form the basis of any future CZP modeling and simulation work.

Change #8

Section 1, paragraph 10:

The primary objectives of the study are to evaluate the PK and safety including the immunogenicity of CZP administered subcutaneously (sc) in children and adolescents with moderate to severe polyarticular-course JIA. The secondary objective of the study is to assess the effectiveness of CZP on the clinical response in children and adolescents with moderate to severe polyarticular-course JIA.

Has been changed to:

The primary objectives of the study are to evaluate the PK and safety including the immunogenicity of CZP administered subcutaneously (sc) in children and adolescents with moderate to severe polyarticular-course JIA. The primary PK and immunological variables are CZP plasma concentrations and anti-CZP antibody levels at Week 16 and Week 48.

Change #9

Section 1, paragraph 11:

The primary safety variable is the incidence of adverse events (AEs). Other safety variables to be assessed are vital signs and measurements of laboratory parameters including hematology, biochemistry, and urinalysis. Physical examination findings (except joint examination) are recorded in the case report form (CRF) only at Screening. Subsequent physical examinations are performed to assess clinically significant changes and thus, only abnormal findings are recorded in the CRF as AEs. Tanner stages (except growth) and growth (height, weight) over the course of the study will be assessed. Autoantibody (antinuclear antibodies [ANA] and anti-double-stranded deoxyribonucleic acid [anti-dsDNA] antibodies) concentrations will be evaluated.

Has been changed to:

The primary safety variables are the incidence of serious treatment-emergent adverse events (TEAEs) and TEAEs leading to permanent withdrawal of IMP. Other safety variables to be assessed are the incidence of TEAEs, vital signs and measurements of laboratory parameters including hematology, biochemistry, and urinalysis. Physical examination findings (except joint examination) are recorded in the case report form (CRF) only at Screening. Subsequent physical examinations are performed to assess clinically significant changes and thus, only abnormal findings are recorded in the CRF as AEs. Tanner stages (except growth) and growth (height, weight) over the course of the study will be assessed. Autoantibody (antinuclear antibodies [ANA] and anti-double-stranded deoxyribonucleic acid [anti-dsDNA] antibodies) concentrations will be evaluated. The secondary objective of the study is to assess the effectiveness of CZP on the clinical response in children and adolescents with moderate to severe polyarticular-course JIA.

Change #10

Section 2, paragraph 2, second sentence:

Juvenile idiopathic arthritis is the most commonly diagnosed rheumatic disease affecting children less than 16 years of age with a prevalence of approximately 100 in 100,000 (Zitelli et al, 2012).

Has been changed to:

Juvenile idiopathic arthritis is the most commonly diagnosed rheumatic disease affecting children less than 16 years of age with a prevalence of approximately 100 in 100,000 children (Zitelli et al, 2012).

Change #11

Section 2, paragraph 12, last sentence:

Other serious AEs that have been infrequently reported in patients treated with currently available TNF-antagonists including CZP include congestive heart failure, drug-induced lupus, new-onset psoriasis, seizures, demyelinating disorders, and pancytopenia.

Has been changed to:

Other serious AEs that have been infrequently reported in patients treated with currently available TNF-antagonists including CZP include congestive heart failure, drug-induced lupus, demyelinating disorders, and pancytopenia.

Change #12

Section 4.1.1:

Certolizumab pegol plasma concentrations and anti-CZP antibody concentrations will be assessed and data will be summarized.

Has been changed to:

Certolizumab pegol plasma concentrations and anti-CZP antibody levels at Week 16 and Week 48 will be assessed and data will be summarized.

Change #13

Section 4.1.2, paragraph 1:

The primary safety variable will be the incidence of AEs.

Has been changed to:

The primary safety variables will be the incidence of serious TEAEs and TEAEs leading to permanent withdrawal of IMP.

Change #14

Section 4.3:

The following text was added:

Other PK and immunological variables are:

- Certolizumab pegol plasma concentrations and anti-CZP antibody levels at other study timepoints

Other safety variables are:

- Incidence of TEAEs, TEAEs of interest, TEAEs by relatedness, TEAEs by severity, and TEAEs by duration of exposure

Change #15

Section 4.3, fifth bullet:

- Assessments of subjects' developmental stages and growth (height, weight) will be performed to determine Tanner stages at Baseline, every 24 weeks thereafter, and the Early Discontinuation/End of Treatment Visit (weight at every visit through Final Visit). Following Protocol Amendment 8, Tanner stages assessment will be performed every 48 weeks, and only for those subjects who have not reached Tanner stage V.

Has been changed to:

- Assessments of study participant's developmental stages and growth (height, weight) will be performed to determine Tanner stages at Baseline, every 24 weeks thereafter, and the Early Discontinuation/End of Treatment Visit (weight at every visit through Final Visit). For study participants enrolled prior to Protocol Amendment 9, Tanner stages assessment will be performed every 48 weeks following Protocol Amendment 8, and only for those subjects who have not reached Tanner stage V.

Change #16

Section 4.3, bullet 15 and 16 under 'other efficacy and health outcome variables':

- Change from Baseline in FPS-R (child-reported, ages 5 to 11 years), daily during the first week of treatment; Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit. Following Protocol Amendment 8, change from Baseline on FPS-R is assessed every 16 weeks.
- Change from Baseline in JIA Pain VAS, daily during the first 7 days of the study (acute and standard versions); and at Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit (standard version) for subjects ages 12 to 17 years. Following Protocol Amendment 8, change from Baseline in JIA Pain VAS is assessed every 16 weeks.

Has been changed to:

- Change from Baseline in FPS-R (child-reported, ages 5 to 11 years), daily during the first week of treatment; Weeks 4, 12, 16, 24, and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit. For study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8.
- Change from Baseline in JIA Pain VAS, daily during the first 7 days of the study (acute and standard versions); and at Weeks 4, 12, 16, 24, and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit (standard version) for study participants ages 12 to 17 years. For study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8.

Change #17

Section 5.1, paragraph 4 and 5 were removed:

An interim analysis of the PedACR30 response rate will be performed after all active subjects have completed the Week 16 (Visit 8) assessments. If less than 50% of the study population enrolled on the reduced CZP dose regimen (Protocol Amendment 5) achieves a PedACR30 response at Week 16, the study will be discontinued.

A full interim analysis will be performed after all active subjects have completed the Week 24 (Visit 10) assessments.

Change #18

Section 5.1, paragraph 6:

A Screening Visit is used to initiate assessments of eligibility. Certolizumab pegol will be administered as a fixed dose based on weight throughout the study (see Table 7-1). At Baseline (Week 0, Visit 2) eligible subjects will begin with 3 loading doses of CZP at Weeks 0, 2, and 4 (minimum=50mg Q2W, maximum=200mg Q2W) followed by a maintenance dose for the duration of the study (minimum=50mg Q4W, maximum=100mg Q2W). Prior to implementation of Protocol Amendments 4 and 5, the minimum and maximum loading doses

in the study were CZP 100mg Q2W and CZP 400mg Q2W, respectively, and the minimum and maximum maintenance doses were CZP 50mg Q2W and CZP 200mg Q2W, respectively. After Week 4 (Visit 5), home based CZP administration by the subject or parent/caregiver will be permitted between scheduled study visits.

Has been changed to:

A Screening Visit is used to initiate assessments of eligibility. Certolizumab pegol will be administered as a fixed dose based on weight throughout the study (see Table 7-1 for doses administered and Section 5.4.2 for the rationale for the different dose regimens). At Baseline (Week 0, Visit 2) eligible study participants will begin with 3 loading doses of CZP at Weeks 0, 2, and 4 followed by a maintenance dose for the duration of the study. After Week 4 (Visit 5), home-based CZP administration by the study participant or parent/caregiver will be permitted between scheduled study visits.

Change #19

Section 5.1, paragraph 7 was removed:

A minimum of 10 subjects will be enrolled on the reduced CZP dose regimen (Protocol Amendment 5) in each weight range of 10 to <20kg (22 to <44lb), 20 to <40kg (44 to <88lb), and ≥40kg (≥88lb). A minimum of 10 subjects will be enrolled in each age category of 2 to 5 years, 6 to 11 years, and 12 to 17 years, irrespective of the dose regimen. A minimum of 25 subjects will be enrolled who receive CZP as monotherapy (ie, subjects with established intolerability or inadequate response to MTX), irrespective of the dose regimen. A minimum of 10 subjects with ERA will be enrolled, irrespective of the dose regimen. Each of these categories is assessed independently.

Change #20

Section 5.1, paragraph 8:

Interim analysis of PK data will compare CZP plasma concentration data from this study with plasma concentrations observed previously in adult subjects with RA. Interim analysis of CZP plasma concentrations was started when 6 subjects in 1 of the age groups completed Week 12 (Visit 7).

Has been changed to:

Interim analyses were performed as described in Section 13.7. A full interim analysis will be performed after all active study participants have completed the Week 24 (Visit 10) assessments.

Change #21

Section 5.1, paragraphs 8 and 9 were removed:

The therapeutic plasma concentration of CZP in children and adolescents is expected to be similar to that required for the adult population (see Section 5.4.2). Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future analyses indicate that plasma concentrations are outside of the exposure range observed in previous studies with

adults, the dosing algorithm may be changed via a protocol amendment. This study will continue during the PK analysis. All subjects assessed in this analysis will continue treatment after Week 12 (Visit 7).

Results of an interim PopPK analysis conducted in Jun 2013 suggest that while observed CZP plasma concentrations have remained in the adult range, they have been at the upper end of the distribution. Simulations predict that for some subjects in RA0043 receiving the originally determined loading doses up to Week 4 (Visit 5), plasma concentrations are likely to exceed the range previously seen in adult subjects receiving CZP 400mg Q2W. Furthermore, plasma concentrations of subjects receiving the originally determined maintenance dose after Week 4 (Visit 5) are predicted to exceed the concentration range observed in adults receiving CZP 200mg Q2W. Based on these findings, the dosing regimen will be changed with Protocol Amendments 4 and 5, and the doses to be administered will be reduced by 50% for all weight groups. This dose change is intended to achieve plasma concentrations that are similar to the effective concentrations observed in previous studies in adult subjects with RA. Continued analysis of CZP plasma concentrations (including additional assessments for subjects undergoing a dose reduction with Protocol Amendment 4) will be performed to confirm that the 50% dose reduction will result in plasma concentrations within the target range of those observed in adults.

Change #22

Section 5.1, paragraph 10:

Pharmacokinetic data from this study (assayed with an enzyme-linked immunosorbent assay [ELISA] technique) will not be used for submission to the Food and Drug Administration (FDA) to complete the Pediatric Research Equity Act commitment, primarily due to some deficiencies detected on the bioanalytical assay used. UCB determined that further collection of additional samples to determine CZP plasma concentrations and anti-CZP antibodies would be of limited utility and an undue burden on the subjects. Following Protocol Amendment 8, these samples will no longer be collected.

Has been changed to:

Pharmacokinetic data from this study that were assayed with an enzyme-linked immunosorbent assay (ELISA) technique will not be used for submission to the Food and Drug Administration (FDA) to complete the Pediatric Research Equity Act commitment, primarily due to deficiencies detected with the use of the bioanalytical assay within RA0043. All study participants enrolled following Protocol Amendment 9 will have plasma concentrations of CZP and anti-CZP antibodies analyzed using an ECLIA method that meets current regulatory standards. In addition, PK and ADA samples (for which sufficient volume is available) collected in this study prior to Protocol Amendment 9 will be analyzed with the ECLIA method. The collective ECLIA-based PK data for this study will form the basis of any future CZP modeling and simulation work.

Change #23

Section 5.1, paragraph 11 was removed:

For the final analysis at the end of the study, UCB will reanalyze all the available samples with sufficient volume with a new Meso Scale Discovery (MSD) bioanalytical assay that is fully validated and that meets current regulatory standards. This PK data, from the re-assayed samples, will be used for final study reporting and thus will not be compared to the previously reported RA adult concentrations, as a different bioanalytical technique was used.

Change #24

Section 5.1.1, paragraph 1, second sentence:

Eligible subjects will subsequently initiate open-label treatment with CZP at Baseline (Week 0, Visit 2) and be permitted to continue until the approval of the marketing application for the polyarticular-course JIA indication in the subject's country or region, or until discontinuation of the study based on the Week 16 analysis of response, or until further notice from UCB.

Has been changed to:

Eligible study participants will subsequently initiate open-label treatment with CZP at Baseline (Week 0, Visit 2) and be permitted to continue until the approval of the marketing application for the polyarticular-course JIA indication in the study participant's country or region, or until further notice from UCB.

Change #25

Section 5.1.1, paragraph 1, last sentence:

Planned Last Subject, First Visit – 1Q/2Q 2015

Has been changed to:

Planned Last Study participant, First Visit – 3Q 2021

Change #26

Section 5.1.2, paragraph 1, first sentence:

Approximately 195 subjects will be screened at about 55 centers in order to enroll 156 subjects in this study.

Has been changed to:

Approximately 195 study participants are planned to be screened at about 55 centers in order to enroll 156 study participants in this study, as follows:

Change #27

Section 5.1.2, paragraph 2 was moved to paragraph 6:

The enrollment per site is limited to a maximum of 12 subjects.

Change #28

Section 5.1.2, bullet 1:

A minimum of 10 subjects will be enrolled on the reduced CZP dose regimen (Protocol Amendment 5) in each weight range of 10 to <20kg (22 to <44lb), 20 to <40kg (44 to <88lb), and ≥40kg (≥88lb)

Has been changed to:

A minimum of 10 study participants will be enrolled on the reduced CZP dose regimen in each weight range of 10 to <20kg (22 to <44lb), 20 to <40kg (44 to <88lb), and ≥40kg (≥88lb) (See Section 7.2 for the doses administered in the study and Section 5.4.2.2 for the rationale for the reduced CZP dose regimen).

Change #29

Section 5.1.2, the following text was added:

Recruitment based on all protocol amendments prior to Protocol Amendment 9 is complete. Following Protocol Amendment 9, an additional 30 study participants will be enrolled on the original dose regimen with the aim to enroll at least 5 study participants in each weight range of 10 to <20kg (22 to <44lb), 20 to <40kg (44 to <88lb), and ≥40kg (≥88lb) (See Section 7.2 for the doses administered in the study and Section 5.4.2.1 for the rationale for the original CZP dose regimen).

Change #30

Section 5.2, Schedule of study assessments, Table 5-1, CZP plasma concentrations and anti-CZP antibodies row

Study period			
Week	**…**	**4, 8, 12, 16, (17(u)), 20, 24**	
Visit (+/-3 days)[a]		**5 to 10**	
…			
CZP plasma concentrations and anti-CZP antibodies		x	
…			

Has been changed to:

Study period			
Week	**…**	**4, 8, 12, 16, (17(u)), 20, 24**	**…**
Visit (+/-3 days)[a]		**5 to 10**	
…			
CZP plasma concentrations		x	
Anti-CZP antibodies		x	
…			

Change #31

Section 5.2, Schedule of study assessments, Table 5-1, footnote f

Height and Tanner stages to be measured at Weeks 24 and 48, every 24 weeks thereafter (Tanner stages will be measured every 48 weeks, and only for subjects who have not reached Tanner stage V following Protocol Amendment 8) and at Early Discontinuation/End of Treatment.

Has been changed to:

Height stages to be measured at Week 24 and 48, every 24 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, Tanner stages assessment will be performed every 48 weeks following Protocol Amendment 8, and only for those subjects who have not reached Tanner stage V) and at Early Discontinuation/End of Treatment.

Change #32

Section 5.2, Schedule of study assessments, Table 5-1, footnote i

TB questionnaire to be completed at Weeks 12 and 24, every 16 weeks thereafter, and Early Discontinuation/End of Treatment. If the Investigator suspects reactivation of latent TB or active TB, TB testing and/or a chest x-ray should be performed as outlined in Section 10.7.9.1.

Has been changed to:

TB questionnaire to be completed at Weeks 12 and 24 and every 16 weeks thereafter, and Early Discontinuation/End of Treatment. If the Investigator suspects reactivation of latent TB or active TB, TB testing and/or a chest x-ray should be performed as outlined in Section 10.7.9.

Change #33

Section 5.2, Schedule of study assessments, Table 5-1, footnote I, sentence 2

If the Investigator suspects reactivation of latent TB or active TB, TB testing and/or a chest x-ray should be performed as outlined in Section 10.7.9.

Has been changed to:

If the Investigator suspects latent TB or active TB, TB testing and/or a chest x-ray should be performed as outlined in Section 10.7.9.

Change #34

Section 5.2, Schedule of study assessments, Table 5-1, footnote j

Analyses will be performed by a central laboratory, except urine dipsticks, which will be done locally at the site. Subjects do not have to be fasting.

Has been changed to:

Hematology/biochemistry/urinalysis will be performed by a central laboratory, except urine dipsticks, which will be done locally at the site. Study participants do not have to be fasting.

Change #35

Section 5.2, Schedule of study assessments, Table 5-1, footnote k

At Screening, laboratory testing includes testing for HBcAb, HBsAb, HBsAg, and HCVAb. In addition, HBV DNA is required for subjects with only positive HBcAb (negative HBsAg and HBsAb) or with only positive HBsAg. Retesting on 1 additional occasion within the Screening Period is allowed in case of isolated exclusionary laboratory results, if, in the Investigator's opinion, the value is not reflective of the subject's previous clinical and laboratory pattern. In addition, retesting within the Screening Period is allowed in case of reporting failure of laboratory results (eg, issues with transportation of samples).

Has been changed to:

At Screening, laboratory testing includes testing for hepatitis B core antibody, hepatitis B surface antibody, hepatitis B surface antigen, hepatitis C virus antibody, and HIV 1/2. Study participants with a positive hepatitis B virus test will not be allowed in the study (except for anti-hepatitis B surface positive only, in case study participant is immune due to well-documented hepatitis B vaccination or isolated false-positive anti-hepatitis B core test confirmed with a confirmatory test such as hepatitis B virus deoxyribonucleic acid [DNA]). A positive hepatitis C antibody test will be confirmed by a confirmatory test (such as hepatitis C virus ribonucleic acid [RNA]) and those with a positive confirmatory test will not be allowed in the study.

Change #36

Section 5.2, Schedule of study assessments, Table 5-1, footnote n

TB screening if not performed within 3 months of Screening: Interferon-gamma release assay (IGRA) testing (QuantiFERON®) is required to be performed by the central lab for all subjects from 5 to 17 years of age. PPD testing is mandatory for subjects from 2 to 4 years of age in this study unless written documentation of BCG vaccination is available (refer to Section 6.2 [exclusion criterion 11] and Section 10.7.9). Following implementation of Protocol Amendment 7, IGRA testing (QuantiFERON) should be done once a year (approximately every 48 weeks) for all subjects from 5 to 17 years of age. For subjects from 2 to 4 years of age, both IGRA and PPD testing should be performed once a year (approximately every 48 weeks). In cases where written documentation of BCG vaccination is available or previous PPD test was positive, only IGRA should be performed (Section 10.7.9.2).

Has been changed to:

TB screening: Interferon-gamma release assay (IGRA) testing (QuantiFERON®) is required to be performed by the central lab for all study participants from 5 to 17 years of age. TST and IGRA testing at Screening is mandatory for study participants less than 5 years of age in this study unless written documentation of BCG vaccination is available (refer to Section 6.2 [exclusion criterion 11] and Section 10.7.9). Following implementation of Protocol Amendment 7, IGRA testing (QuantiFERON) should be done once a year (approximately every 48 weeks) for all study participants.

Change #37

Section 5.2, Schedule of study assessments, Table 5-1, footnote o

A chest radiograph (anterior-posterior view at minimum, but preferably anterior-posterior and lateral) must be taken if the subject has a positive IGRA/PPD testing at Screening or, if written documentation of BCG vaccination is available for subjects ages 2 to 4 years, a TB questionnaire indicating an increased subject's risk of exposure or infection with TB. If a subject has had a recent radiograph of the chest within approximately 3 months prior to Screening, it may be used in lieu of the protocol-required radiograph. All chest imaging must be read by a qualified radiologist/pulmonary physician who is specifically required to look for evidence of active TB or inactive TB. Refer to Section 10.7.9.2.2 for further information on chest x-rays.

Has been changed to:

Chest radiographic imaging is done at Screening and results must be available at Baseline before first drug administration unless as chest x-ray or CT is available within 2 months prior to Screening.

Change #38

Section 5.2, Schedule of study assessments, Table 5-1, footnote q

For subjects ages 5 to 11 years. Daily assessment during the first week (Baseline and Day 1 to Day 7, to be collected at Week 1). In addition, to be completed at Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (every 16 weeks following Protocol Amendment 8) through the End of Treatment/Early Discontinuation Visit.

Has been changed to:

For study participants ages 5 to 11 years. Daily assessment during the first week (Baseline and Day 1 to Day 7, to be collected at Week 1). In addition, to be completed at Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) through the End of Treatment/Early Discontinuation Visit.

Change #39

Section 5.2, Schedule of study assessments, Table 5-1, footnote r

For subjects ages 12 to 17 years. Daily assessment of acute VAS version during the first week (at Baseline and Day 1 to Day 7, to be collected at Week 1). In addition, standard VAS version to be completed at Baseline, Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (every 16 weeks following Protocol Amendment 8) through the End of Treatment/Early Discontinuation Visit for subjects ages 12 to 17 years.

Has been changed to:

For study participants ages 12 to 17 years. Daily assessment of acute VAS version during the first week (at Baseline and Day 1 to Day 7, to be collected at Week 1). In addition, standard VAS version to be completed at Baseline, Weeks 4, 12, 16, 24, and then every 8 weeks

thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) through the End of Treatment/Early Discontinuation Visit for study participants ages 12 to 17 years.

Change #40

Section 5.2, Schedule of study assessments, Table 5-1, footnote u

CZP plasma concentration and anti-CZP antibodies to be measured at Weeks 4, 12, 16, and 24. A postdose CZP plasma sample will be collected at approximately 5 to 7 days following the Week 16 Visit (ie, requires an additional clinic site visit for blood collection at Week 17). For subjects already enrolled and treated prior to the implementation of Protocol Amendment 4 and hence undergoing a reduction of their dose, additional PK samples will be collected prior to dosing at the visit the dose change occurs and at the next 3 site visits following the dose change, ie, additional PK samples will be collected at the Unscheduled Visits or at the regular visits if not already planned per regular schedule. Afterwards, the regular PK sampling schedule applies

Has been changed to:

CZP plasma concentration and anti-CZP antibodies to be measured at Weeks 4, 12, 16, and 24. A postdose CZP plasma sample will be collected at approximately 5 to 7 days following the Week 16 Visit (ie, requires an additional clinic site visit for blood collection at Week 17). Samples for CZP plasma concentration and anti-CZP antibodies will be collected as separate samples.

Change #41

Section 5.2, Schedule of study assessments, Table 5-1, footnote v

CZP plasma concentration and anti-CZP antibodies to be measured at Weeks 32, 40, and 48 and every 24 weeks thereafter. For subjects already enrolled and treated prior to the implementation of Protocol Amendment 4 and hence undergoing a reduction of their dose, additional PK samples will be collected prior to dosing at the visit the dose change occurs and at the next 3 site visits following the dose change, ie, additional PK samples will be collected at the Unscheduled Visits or at the regular visits if not already planned per regular schedule. Afterwards, the regular PK sampling schedule applies. Following Protocol Amendment 8, samples for CZP plasma concentration and anti-CZP antibodies will no longer be collected.

Has been changed to:

CZP plasma concentration and anti-CZP antibodies to be measured at Weeks 32, 40, 48, and every 24 weeks thereafter for study participants enrolled following Protocol Amendment 9. For study participants enrolled prior to Protocol Amendment 9, samples for CZP plasma concentration and anti-CZP antibodies will no longer be collected. Samples for CZP plasma concentration and anti-CZP antibodies will be collected as separate samples.

Change #42

Section 5.2, Schedule of study assessments, Table 5-1, footnote z

Following Protocol Amendment 8, on-site CZP administration, safety sampling, and efficacy assessment frequency changes to every 16 weeks instead of every 8 weeks, if administration at home is feasible. The option to come to the site for CZP administration between scheduled visits is available as needed.

Has been changed to:

For study participants enrolled prior to Protocol Amendment 9, on-site CZP administration, safety sampling, and efficacy assessment frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8, provided that compliance is maintained with the CZP dosing schedule using at-home administration. The option to come to the site for CZP administration between scheduled visits is available as needed.

Change #43

Section 5.3, Schematic diagram, footnote a

Following Protocol Amendment 8, visits will be every 16 weeks instead of every 8 weeks.

Has been changed to:

Following Week 32, visits will be every 8 weeks. For study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8.

Change #44

Section 5.3, Schematic diagram, footnote b has been added

The futility analysis of PedACR30 after all study participants on the reduced CZP dose completed Week 16 has already been completed. A further futility analysis will not be performed using the additional study participants that will be enrolled on the original CZP dose regimen following the implementation of Protocol Amendment 9.

Change #45

Section 5.4.1, paragraph 3, sentence 3:

In light of these results and the efficacy of CZP demonstrated in the 4 adequate and well-controlled studies in adult RA, it is appropriate to extrapolate these efficacy data to the intended JIA population if similar results are obtained for PK and safety in JIA as seen for adult RA. The opinion within the pediatric rheumatology community supports that extrapolation from open-label PK/safety data is acceptable for additional members of the class of TNF-antagonists.

Has been changed to:

Through extensive interactions between the FDA and external experts, culminating in a collaborative workshop in October 2019 entitled “Accelerating Drug Development for

polyarticular Juvenile Idiopathic Arthritis (pJIA)", a therapeutic bridging approach from RA to pJIA was strongly supported for TNF-α inhibitors based on the relationship between RA and pJIA and the extensive knowledge of TNF-α inhibitors as therapeutic agents in these two populations. This approach (based on "Pharmacokinetic (PK) matching") directs that the therapeutic effect of TNF-α inhibitors (such as CZP) in pJIA patients can be expected if the pediatric systemic exposure for the drug is within the therapeutic range for adult RA patients.

Change #46

Section 5.4.1, the following text was added:

Study RA0043 is being undertaken in support of the pJIA Pediatric Research Equity Act (PREA) requirement for CZP. The pJIA development program for CZP will be based on PK data generated with the newly validated MSD ECLIA method for pediatric study participants in (Section 7.2 and Section 5.4.2). To enable this approach, an additional 30 study participants will be enrolled in RA0043 following Protocol Amendment 9 at the original CZP dosing regimen.

Central to application of this approach is the existence of a reference systemic exposure (PK) range which is associated with therapeutic benefit of the drug in adult RA population. A supporting adult reference PK dataset for "PK matching" in the pJIA program will also need to be based on data generated with the ECLIA method. Accordingly, a separate study is being undertaken in order to generate ECLIA-based CZP PK data for CZP in adults with RA.

Change #47

Section 5.4.2, the following text was added:

The original minimum and maximum loading doses in the study were CZP 100mg Q2W and CZP 400mg Q2W, respectively, and the original minimum and maximum maintenance doses were CZP 50mg Q2W and CZP 200mg Q2W, respectively (see Section 5.4.2.1 for the rationale for the original CZP dose regimen). Based on an interim PopPK analysis of RA0043 data, the minimum and maximum loading doses in the study were adjusted to CZP 50mg Q2W and CZP 200mg Q2W, respectively, and the minimum and maximum maintenance doses were adjusted to CZP 50mg Q4W and CZP 100mg Q2W, respectively, following implementation of Protocol Amendments 4 and 5 (see Section 5.4.2.2 for the rationale for the reduced CZP dose regimen).

However, it was later determined that there were deficiencies detected with the use of the bioanalytical assay within RA0043, which rendered the PK data for the PopPK analysis and simulations that informed the dose reduction in Protocol Amendment 4 and 5 unusable from a regulatory standpoint. Accordingly, PK samples were no longer collected for study participants on the reduced CZP dose regimen following implementation of Protocol Amendment 8.

An ECLIA method, for which selectivity had previously been assessed in the RA matrix, has now been validated to meet the standards set in the regulatory guidance for analytical procedures and methods validations for drugs and biologics (FDA, Guidance for Industry – Bioanalytical Method Validation, 2018). The ECLIA assay consists of a homogeneous bridging immunoassay on the MSD platform.

Based on 24-week interim results from RA0043 (Section 13.7), both the original and reduced dose regimens showed safety profiles similar to the approved CZP dose regimen in the adult RA population. The overall clinical response in the study (taking both dose regimens into account) was PedACR30 and PedACR50 responses of 77.3% and 67.5%, respectively at Week 12. The response from the original dose regimen was 75.6% for PedACR30 and 64.1% for PedACR50. PedACR50 response demonstrates a highly clinically relevant decrease in disease activity.

Therefore, in order to adequately assess the exposure levels and clinical experience of CZP in pJIA at both the reduced and original CZP dose regimens and also adequately support the safety assessment of the original CZP dosing regimen, as more of the safety data collected in the study to date has been on the reduced dose, 30 additional study participants will be enrolled on the original CZP dose regimen following Protocol Amendment 9. All study participants enrolled following Protocol Amendment 9 will have plasma concentrations of CZP and anti-CZP antibodies analyzed using the ECLIA method. In addition, PK and ADA samples (for which sufficient volume is available) collected in this study prior to Protocol Amendment 9 will be analyzed with the ECLIA method. The collective ECLIA-based PK data for this study will form the basis of any future CZP modeling and simulation work.

Change #48

Section 5.4.2, the Section 5.4.2.1 and Section 5.4.2.2 headings were added.

Change #49

Section 5.4.2, paragraph 3; the following text was moved to Section 5.4.2.2:

During the course of the study, results from the ongoing interim PK analysis and an interim PopPK analysis conducted in Jun 2013 indicated that plasma concentrations within the range previously seen in adult subjects receiving CZP 200mg Q2W would be achieved if the dose in RA0043 was reduced to 50% of the original dose used in the study. Therefore, the maintenance doses in this study will be reduced further with Protocol Amendment 4 so that subjects with body weights between 20 and <40kg (44 to <88lb) will receive CZP 50mg Q2W, and subjects with body weights of ≥40kg (≥88lb) will receive CZP 100mg Q2W (see Table 7-1). The optimal maintenance dose estimated in the PopPK model for the lowest weight group would be CZP 25mg Q2W, however, the lowest available dose size is CZP 50mg. Thus, subjects with body weights of 10 to <20kg (22 to <44lb) will receive CZP 50mg Q4W to achieve this 50% reduction. In addition, with Protocol Amendment 5, the loading dose in the study will be reduced by 50% for newly enrolled subjects, so that subjects with body weights of 10 to <20kg (22 to <44lb) will receive CZP 50mg at Weeks 0, 2, and 4, subjects with body weights between 20 to <40kg (44 to <88lb) will receive CZP 100mg at Weeks 0, 2, and 4, and subjects with body weights ≥40kg (≥88lb) will receive CZP 200mg at Weeks 0, 2, and 4.

The rationale behind selecting the equivalent of the adult therapeutic dose is based on the following:

- There is no metabolic rationale to expect a difference in the PK/PD of CZP in a younger population, particularly as there is no involvement of cytochrome P450.

- Evaluation of a previous anti-TNF antibody (CDP571, a whole antibody) in a pediatric population (administered iv) confirmed that the PK and safety were similar to that of an adult population.
- Doses in excess of CZP 400mg (up to CZP 800mg) have been administered to healthy adult subjects and subjects with RA without any dose-limiting toxicities being identified.
- A conservative approach to dose reduction was chosen because the body weight of pediatric subjects may be influenced largely by frame size while the range of body weight of adults may be more influenced by percent body fat.

Change #50

Section 5.4.2.1, paragraph 4, first sentence:

The original choice of dose and the weight-based dose-adjustment algorithm, prior to Protocol Amendments 4 and 5, was supported by simulations of the PK exposure and response rates in children using the PopPK model and PK/PD exposure response model developed in adult RA subjects, corrected for pediatric demographics (C87079 addendum 08 Oct 2008).

Has been changed to:

The original choice of dose and the weight-based dose-adjustment algorithm was supported by simulations of the PK exposure and response rates in children using the PopPK model and PK/PD exposure response model developed in adult RA study participants, corrected for pediatric demographics (C87079 addendum 08 Oct 2008).

Change #51

Section 5.4.2, paragraph 4, sentence 5 was removed:

The revised dose and weight-based dose adjustment algorithm was based on a PopPK analysis and simulation using data from 35 subjects in this study with post-Baseline plasma concentrations of CZP available prior to Protocol Amendments 4 and 5.

Change #52

Section 5.4.2, the following text was added within Section 5.4.2.1:

The original CZP dose regimen is the regimen that will be used for study participants enrolled following Protocol Amendment 9

Change #53

Section 5.4.2, the following text was added within Section 5.4.2.2:

Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future analyses indicate that plasma concentrations were outside of the exposure range of those observed in previous studies with adults, the dosing algorithm could have been changed via a protocol amendment, and if necessary additional interim analyses including PopPK, could have been performed.

Change #54

Section 5.4.2, the following text was added within Section 5.4.2.2:

However, it was later determined that there were deficiencies detected with the use of the bioanalytical assay within RA0043, which rendered the PK data for the PopPK analysis and simulations that informed the dose reduction in Protocol Amendment 4 and 5 unusable from a regulatory standpoint. Study participants enrolled prior to the implementation of Protocol Amendment 9 can remain on the reduced CZP dose or may be switched to the original CZP dose at the discretion of the Investigator and in consultation with the medical monitor. Additional dose changes are not allowed (Section 7.2.1).

Change #55

Section 6.2, exclusion criterion 11:

Subjects with known TB infection, or at high risk of acquiring TB infection, are excluded. Subjects with latent TB (LTB) infection that have not received a minimum of 4 weeks of prophylactic treatment are only eligible following prophylaxis:

a. Known TB infection whether present or past is defined as:
    - Active TB infection or clinical signs and symptoms suspicious for TB (pulmonary or extra-pulmonary)
    - History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection
    - Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the subject's medical history

b. High risk of acquiring TB infection is defined as:
    - Known exposure of Subject or Caregiver to another person with active TB infection within the 3 months prior to Screening
    - Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection to Subject or Caregiver is high

c. Latent TB infection is defined as:

    Absence of signs, symptoms (ie, evidence of organ-specific involvement), or physical findings suggestive of TB infection with a positive interferon-gamma release assay (IGRA [QuantiFERON]) test (or 2 indeterminate IGRA test results) or positive PPD (where the PPD skin test is approved for use by UCB; mandatory for ages 2 to 4 years in this study) or, if written documentation of Bacille Calmette-Guérin (BCG) vaccination is available for subjects ages 2 to 4 years, a TB questionnaire indicating an increased subject's risk of exposure or infection with TB, and a chest x-ray (or other imaging) without evidence of TB infection.

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

Refer to Section 10.7.9 for additional information on TB definition and clinical signs, diagnosis, documentation, and treatment.

Subjects with a history of or active infection with nontuberculous mycobacteria (NTMB) are excluded from this study.

Has been changed to:

Participant has:

a. Known active TB disease
b. History of active TB involving any organ system
c. History of or current latent tuberculosis infection (LTBI)
d. High risk of exposure to TB infection
e. Current nontuberculous mycobacterial (NTMB) infection or history of NTMB infection. For further information relating to definitions of known active TB, past history of TB, LTBI, high risk of acquiring TB infection and NTMB infection refer to Section 10.7.9 (Assessment and management of TB and TB risk factors).

Change #56

Section 6.2, exclusion criterion 13:

Subject with known concurrent viral hepatitis or known positivity for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody or known human immunodeficiency virus (HIV) infection. At Screening, a hepatitis panel result which indicates immunity due to hepatitis B vaccination is not considered an exclusion criterion.

Has been changed to:

Study participant has a history of or current hepatitis B or C virus or HIV 1/2 or has any of the following laboratory abnormalities during the screening period:

a. Hepatitis B surface (HBs) antigen, hepatitis B core (HBc) antibody (except for isolated, false-positive anti-HBc confirmed with a confirmatory test such as hepatitis B virus [HBV]-deoxyribonucleic acid [DNA] [refer to Table 5-1 footnote k and Section 10.6 (Clinical Laboratory Tests) table footnote c]): Positive to any of these
b. Hepatitis C virus (HCV) positive: defined as hepatitis C antibody (anti-HCV Ab) positive confirmed via a confirmatory test (for example, HCV polymerase chain reaction).
c. HIV antigen or antibody: Positive to either test

Change #57

Section 6.2, exclusion criterion 17, sentence 2, 3, and 4:

For postmenarcheal female study participants not currently sexually active, the study participant and parent or legal representative should agree that the study participant will employ an effective means of birth control should the study participant become sexually active. Adequate methods of birth control are: oral/parenteral/implantable hormonal contraceptives (stable at least 2 months prior to Screening (Visit 1) if initiated prior to entering the study) or a combination of barrier and spermicide. Study participants must agree to use adequate contraception during the study and for 12 weeks after their last dose of study medication (or longer if required by local regulations).

Has been changed to:

For postmenarcheal female study participants not currently sexually active, the study participant and parent or legal representative should agree that the study participant will employ an effective means of birth control consistently and correctly should the study participant become sexually active. Effective methods of birth control are: oral/parenteral/implantable hormonal contraceptives (stable at least 2 months prior to Screening (Visit 1) if initiated prior to entering the study) or a combination of barrier and spermicide. Study participants must agree to use effective contraception during the study and for 12 weeks after their last dose of study medication (or longer if required by local regulations).

Change #59

Section 6.3, paragraph 2, bullet 3 was removed:

Subjects with LTB infection, indicated by positive PPD skin test or positive IGRA test result (or TB questionnaire indicating an increased risk of exposure or infection with TB for subjects ages 2 to 4 years with documented BCG vaccination) and a chest imaging without evidence of TB infection at Screening, may be rescreened after initiation of treatment for latent TB. Prior to first study medication administration, TB treatment must have been ongoing for at least 4 weeks before enrollment will be allowed and after approval of the Medical Monitor. Treatment for TB must be continued until completion of 9 months of therapy (refer to Section 10.7.9).

Change #60

Section 6.4, the following text for Liver Chemistry Stopping Criteria was added:

Participants with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should be discontinued. The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Participants with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Participants with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, and eosinophilia (ie, >5%).

The PDILI criterion below allows participants to continue on IMP at the discretion of the investigator:

- Participants with ALT or AST ≥3xULN (and ≥2x baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 17.10. If participants are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on participants in the case of IMP discontinuation to complete the final evaluation. Participants with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

Change #61

Section 6.5, Withdrawal criteria, the following text was added:

Study participants are free to withdraw from the study at any time, without prejudice to their continued care. Where possible, study participants discontinuing study medication should be encouraged to remain in the study.

A study participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the study participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a study participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Change #62

Section 6.5, withdrawal criteria 3 and 4:

3) Subject who develops active TB or NTMB infection during the study must be withdrawn (refer to Section 10.7.9).

4) Subject who prematurely discontinues treatment for LTB, or, in the opinion of the Investigator or Sponsor, is noncompliant with anti-TB therapy must be withdrawn.

Has been changed to:

A study participant considered as having either a suspected new LTBI or who develops active TB or NTMB infection during the study (including but not limited to, conversion demonstrated by interferon-gamma release assay (IGRA) or other diagnostic means) must be immediately discontinued from IMP (refer to Section 10.7.9.8 for further details).

a. The study participant must be permanently withdrawn from the study if further examinations result in a diagnosis of active TB, NTMB infection or if the study participant is diagnosed with LTBI. An Early Discontinuation visit must be scheduled as soon as possible, but not later than the next regular visit.

b. Any confirmed diagnosis or suspicion of a latent or active TB infection is a reportable event. Either type of infection must be reported as an adverse event of special interest (AESI) and must be captured on an AE report form, ticking the appropriate AESI and, if applicable, serious adverse event (SAE) field(s) on the form to clearly indicate the level of seriousness. A UCB TB follow-up form also must be completed. Confirmed active TB is an SAE and must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirements until such time as the TB infection resolves.

Change #63

Section 6.5, withdrawal criteria 2, 3, 4, and 6:

Subjects should be withdrawn from the study if any of the following events occur:

2) Subject/caregiver is noncompliant with the study procedures or medications in the opinion of the Investigator or Sponsor.

3) Subject who develops active TB or NTMB infection during the study must be withdrawn (refer to Section 10.7.9).

4) Subject who prematurely discontinues treatment for LTB, or, in the opinion of the Investigator or Sponsor, is noncompliant with anti-TB therapy must be withdrawn.

5) Subject is found to be persistently noncompliant (missing 2 or more consecutive scheduled CZP doses or missing 3 or more doses over a 12-month period), the Sponsor in conjunction with the Investigator will make a decision as to whether the subject should be withdrawn from the study (see Section 7.7).
This rule does not apply when CZP is discontinued if the subject is in CRM or if CZP is temporarily discontinued due to an AE. In the case of temporary discontinuation due to an AE, the Sponsor in conjunction with the Investigator will make a decision as to whether the subject should be withdrawn from the study.

6) Subject takes prohibited concomitant medications as defined in this protocol (see Section 7.8.3).

Has been changed to:

Study participants must be permanently discontinued from study medication (but not necessarily from the study) if any of the following occurs:

1. Study participant/caregiver is noncompliant with the study procedures or medications in the opinion of the Investigator or Sponsor.
2. A study participant considered as having either a suspected new LTBI or who develops active TB or NTMB infection during the study (including but not limited to, conversion demonstrated by interferon-gamma release assay (IGRA) or other diagnostic means) must be immediately discontinued from IMP (refer to Section 10.7.9.8 for further details).
   a) The study participant must be permanently withdrawn from the study if further examinations result in a diagnosis of active TB, NTMB infection or if the study participant is diagnosed with LTBI. An Early Discontinuation visit must be scheduled as soon as possible, but not later than the next regular visit.
3. Study participant is found to be persistently noncompliant (missing 2 or more consecutive scheduled CZP doses or missing 3 or more doses over a 12-month period), the Sponsor in conjunction with the Investigator will make a decision as to whether the study participant should be withdrawn from the study (see Section 7.7).
   This rule does not apply when CZP is discontinued if the study participant is in CRM or if CZP is temporarily discontinued due to an AE. In the case of temporary discontinuation due to an AE, the Sponsor in conjunction with the Investigator will make a decision as to whether the study participant should be withdrawn from the study.
4. Study participant takes prohibited concomitant medications as defined in this protocol (see Section 7.8.3).

Change #64

Section 6.5, withdrawal criteria 1 and 8:

Subjects should be withdrawn from the study if any of the following events occur:

1. Subject develops an illness that would interfere with continued participation (eg, malignancies).
8. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.

Has been changed to:

Study participants may be discontinued from study medication (but not necessarily from the study) if any of the following occurs, but may be restarted after consultation with the Medical Monitor:

1. Study participant develops an illness that would interfere with continued participation (eg, malignancies).
2. If there is a positive pregnancy test, study medication will be held. If there is confirmed pregnancy, study medication must be discontinued until end of the pregnancy. In case the

study participant intends to breastfeed after a pregnancy study medication must be further discontinued until end of breastfeeding.

Change #65

Section 6.5, withdrawal criteria 7 and 9:

Subjects should be withdrawn from the study if any of the following events occur:

7. Subject/legal representative withdraws consent.
9. The Sponsor or a regulatory agency requests withdrawal of the subject..

Has been changed to:

Study participants should be withdrawn from the study if any of the following events occur:

1. Study participant or legal representative withdraws his/her consent.
2. The sponsor or a regulatory agency requests withdrawal of the study participant.

Change #66

Section 7.2, paragraph 1, sentence 1 and 2:

Throughout the study, CZP dosing is fixed dose based on weight and given Q2W, with exception of the lowest weight group, who will receive the maintenance dose Q4W following implementation of Protocol Amendment 4. The range of exposures in each weight category is presented in Table 7-1. Subjects start with 3 loading doses of CZP at Weeks 0, 2, and 4 (minimum=50mg Q2W, maximum=200mg Q2W) followed by a maintenance dose for the duration of the study (minimum=50mg Q4W, maximum=100mg Q2W).

Has been changed to:

Throughout the study, CZP dosing is fixed dose based on weight and given Q2W, with exception of the lowest weight group on the reduced CZP regimen who will receive the maintenance dose Q4W. The loading dose, maintenance dose, and range of exposures in each weight category for both the original and reduced CZP regimens are presented in Table 7-1.

Change #67

Section 7.2, Table 7-1, the following was added:

Table 17-1 Dosing administration of CZP[a]

Weight range	Loading dose – Weeks 0, 2, and 4 (mg/kg dose range) IMP Description	Maintenance – Week 6 and onwards (mg/kg dose range) IMP Description
Original CZP regimen		
10 to <20kg (22 to <44lb)	100mg Q2W (5-10mg/kg) 1 x 0.5mL inj	50mg Q2W (2.5-5mg/kg) 1 x 0.25 mL inj
20 to <40kg (44 to <88lb)	200mg Q2W (5-10mg/kg) 1 x 1mL inj	100mg Q2W (2.5-5mg/kg) 1 x 0.5mL inj
≥40kg (≥88lb)	400mg Q2W (<10mg/kg) 2 x 1mL inj	200mg Q2W (<5mg/kg) 1 x 1mL inj

Change #68

Section 7.2, Table 7-1, footnote a:

Note that Table 7-1 describes the dosing administration of CZP after implementation of Protocol Amendments 4 and 5. Refer to Section 7.2.1 for the procedure to be taken for subjects already enrolled and treated prior to the implementation of Protocol Amendment 4, and who are undergoing a dose change.

Has been changed to:

Note that the original CZP regimen describes the dosing administration of CZP prior to the implementation of Protocol Amendments 4 and 5 and for study participants enrolled following the implementation of Protocol Amendment 9. The reduced CZP regimen describes the dosing administration of CZP after implementation of Protocol Amendments 4 and 5. Refer to Section 7.2.1 for the procedure to be taken for study participants who are undergoing a dose change.

Change #69

Section 7.2, paragraph 5, sentence 1 has been moved to the 4th sentence position:

Prior to CZP administration at home, study participants/caregivers will be trained by the site staff and provided written instructions on the fixed dose for injection and the correct sc injection technique including 0.25mL, 0.5mL, and 1mL injections, as appropriate.

Change #70

Section 7.2, paragraph 7, last sentence:

Subjects not maintaining persistent CID following achievement of CRM and resuming treatment will restart the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a maintenance dose administered Q2W, or Q4W for the lowest weight group after implementation of Protocol Amendment 4, for the duration of the study.

Has been changed to:

Study participants not maintaining persistent CID following achievement of CRM and resuming treatment will restart the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a maintenance dose administered Q2W, or Q4W for the lowest weight group on the reduced CZP regimen for the duration of the study.

Change #71

Section 7.2.1, paragraph 1:

With Protocol Amendment 4, the maintenance dose in the study will be reduced by 50% for all weight groups (not applicable for subjects enrolled on the reduced CZP dose regimen per Protocol Amendment 5).

Has been changed to:

Following Protocol Amendment 9, study participants will only be enrolled on the original CZP dose regimen. With Protocol Amendment 4, the maintenance dose in the study was reduced by 50% for all weight groups (not applicable for study participants enrolled on the reduced CZP dose regimen per Protocol Amendment 5). Participants on the reduced CZP dose regimen can remain on the reduced CZP dose or may be switched to the original CZP dose regimen at the discretion of the Investigator and in consultation with the medical monitor. Additional dose changes are not allowed. The procedure for dose change is as follows.

Change #72

Section 7.2.1, bullet 2, sub-bullets 1 and 2 have been deleted:

- For subjects undergoing a dose change prior to or at Week 12 (Visit 8), and who return for regularly scheduled visits every 4 weeks for a period of 12 weeks after the dose change, no additional Unscheduled Visits will be required.
- For subjects undergoing a dose change after Week 12 (Visit 8), 1 or 2 additional Unscheduled Visits will be required. For example, a subject undergoing a dose change at Week 20 (Visit 9) will return for a regularly scheduled visit at Week 24 (Visit 10), will require an additional Unscheduled Visit at Week 28, and will return for the next regularly scheduled visit at Week 32 (Visit 11). A subject who is undergoing a dose change at Week 40 (Visit 12) will require an Unscheduled Visit at Week 44, will

return for a regularly scheduled visit at Week 48 (Visit 13), and will require another Unscheduled Visit at Week 52.

Change #73

Section 7.2.1, bullet 2, sub-bullet 3, sentence 3 has been deleted:

– For example, a subject undergoing the dose change at Week 42 at the clinic will return for an Unscheduled Visit at Week 46, then continue with the regular visit at Week 48 (Visit 13), and return for an additional Unscheduled Visit at Week 52 before continuing with the regular Week 56 visit (Visit 14).

Change #74

Section 7.2.1, bullet 4 has been deleted:

- A predose PK sample will be collected prior to administration of CZP at the visit the dose change occurs. Additional predose PK sampling after the change in dose will be performed at the next 3 site visits, ie, additional PK samples will be collected at the Unscheduled Visits or at the regular visit if not already planned per regular schedule.

Change #75

Section 7.8.3, paragraph 1 bullet 1:

- Nonbiologic DMARDs (other than MTX; see Section 7.8.1) and biologic DMARDs (eg, anakinra, rilonacept, etanercept, adalimumab, infliximab, golimumab, rituximab, abatacept, tocilizumab, CZP other than study medication)

Has been changed to:

- Nonbiologic DMARDs (other than MTX; see Section 7.8.1) and biologic DMARDs

Change #76

Section 7.9 (Lost to Follow up) was added:

Change #77

Section 8.1, paragraph 1 sentence 1:

Prior to any study activities and 4 days prior to the Baseline Visit (Visit 2), subjects and parent(s)/legal representative, as applicable, will be asked to read and sign an Informed Consent/Assent Form that has been approved by an IRB/IEC and which complies with regulatory requirements.

Has been changed to:

Prior to any study activities and at least 4 days prior to the Baseline Visit (Visit 2), study participants and parent(s)/legal representative, as applicable, will be asked to read and sign an Informed Consent/Assent Form that has been approved by an IRB/IEC and which complies with regulatory requirements.

Change #78

Section 8.1, paragraph 2 bullet 15:

Chest x-ray (only for subjects with positive IGRA or PPD testing)**

Has been changed to:

Chest radiographic imaging and results must be available at Baseline before first IMP administration unless a chest X-ray or CT scan is available from 2 months prior to Screening.

Change #79

Section 8.1, paragraph 2 bullet 16:

TB screening if not performed within 3 months of Screening: PPD skin test for subjects from 2 to 4 years of age (unless written documentation for BCG vaccination is available) or IGRA (to be performed by the central lab) for subjects from 5 to 17 years of age**

Has been changed to:

TB screening: TST and IGRA for study participants from 2 to 4 years of age (unless the study participant is located in a country with high TST positivity and/or written documentation for BCG vaccination is available) or IGRA (to be performed by the central lab) for study participants from 5 to 17 years of age. Note that the TST may be positive due to BCG vaccination, however, UCB will not permit enrollment of pediatric study participants <5 years old into the study without written approval from a physician with expertise in pediatric TB**

Change #80

Section 8.2

- CZP plasma concentrations and anti-CZP antibodies

Has been changed to:

- CZP plasma concentrations
- Anti-CZP antibodies

Change #81

Section 8.3

- CZP plasma concentrations and anti-CZP antibodies(Week 1 only)

Has been changed to:

- CZP plasma concentrations (Week 1 only)
- Anti-CZP antibodies (Week 1 only)

Change #82

Section 8.4

- CZP plasma concentrations and anti-CZP antibodies (Weeks 4, 12, 16, and 24 only, OR if a dose change is performed at the current visit OR if the subject's dose was changed during 1 of the last 3 visits following Protocol Amendment 4; predose.
  Subjects will return to the clinic site for a **postdose CZP plasma sample** approximately **5 to 7 days following the Week 16 visit**.)

Has been changed to:

- CZP plasma concentrations (predose at Weeks 4, 12, 16, and 24.
  Study participants will return to the clinic site for a **postdose CZP plasma sample** approximately **5 to 7 days following the Week 16 visit**.)
- Anti-CZP antibodies (predose at Weeks 4, 12, 16, and 24)

Change #83

Section 8.4, last paragraph

Documentation of the **Week 16 and Week 24** assessment of all 6 core set measures of PedACR response (PRINTO/PRCSG standard joint examination, Physician's Global Assessment of Disease Activity [VAS], CHAQ-parent reported, Parent's Assessment of Arthritis Pain [VAS], Parent's Global Assessment of Overall Well-Being [VAS] and CRP) **will be submitted to UCB or designee for immediate review of completeness, while the subject is still on site.**

Has been changed to:

Documentation of the **Week 24** assessment of all 6 core set measures of PedACR response (PRINTO/PRCSG standard joint examination, Physician's Global Assessment of Disease Activity [VAS], CHAQ-parent reported, Parent's Assessment of Arthritis Pain [VAS], Parent's Global Assessment of Overall Well-Being [VAS] and CRP) **will be submitted to UCB or designee for immediate review of completeness, while the study participant is still on site.**

Change #84

Section 8.5, heading

Visits 11 and continuing (Week 32 and every 8 weeks thereafter [every 16 weeks following Protocol Amendment 8])

Has been changed to:

Visits 11 and continuing (Week 32 and every 8 weeks thereafter)

Change #85

Section 8.5, the following paragraph has been added

For study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol

Amendment 8, provided that compliance is maintained with the CZP dosing schedule using at-home administration.

Change #86

Section 8.5, bullet 2

Height (Week 48 and every 24 weeks thereafter [every 48 weeks following Protocol Amendment 8])

Has been changed to:

Height (Week 48 and every 24 weeks thereafter; for study participants enrolled prior to Protocol Amendment 9, height assessment will be performed every 48 weeks following Protocol Amendment 8)

Change #87

Section 8.5, bullet 4

Tanner stages (except growth; Week 48 and every 24 weeks thereafter [every 48 weeks and only for subjects who have not reached Tanner stage V following Protocol Amendment 8])

Has been changed to:

Tanner stages (except growth; for study participants enrolled prior to Protocol Amendment 9, Tanner stages assessment will be performed every 48 weeks following Protocol Amendment 8, and only for those subjects who have not reached Tanner stage V)

Change #88

Section 8.5, bullet 6

TB screening once a year (approximately every 48 weeks)

Has been changed to:

TB screening once a year (at least every 48 weeks)

Change #89

Section 8.5, bullet 28

- CZP plasma concentrations and anti-CZP antibodies (Weeks 32, 40, and 48 and every 24 weeks thereafter, OR if a dose change is performed at the current visit OR if the subject's dose was changed during 1 of the last 3 visits following Protocol Amendment 4; following Protocol Amendment 8, these samples will no longer be collected)

Has been changed to:

- CZP plasma concentrations (for study participants enrolled following Protocol Amendment 9 only; Weeks 32, 40, and 48 and every 24 weeks thereafter)
- Anti-CZP antibodies (for study participants enrolled following Protocol Amendment 9 only; Weeks 32, 40, and 48 and every 24 weeks thereafter)

Change #90

Section 8.6.1, the following paragraph has been removed:

Documentation of the **Week 56** assessment of all 6 core set measures of PedACR response (PRINTO/PRCSG standard joint examination, Physician's Global Assessment of Disease Activity [VAS], CHAQ-parent reported, Parent's Assessment of Arthritis Pain [VAS], Parent's Global Assessment of Overall Well-Being [VAS] and CRP) **will be submitted to UCB or designee for immediate review of completeness, while the subject is still on site.**

Change #91

Section 8.6.1, the following sentence has been added:

If required, study participants will return for an Unscheduled Visit to undergo the dose change.

Change #92

Section 8.6.1, the following assessment has been removed:

- CZP plasma concentrations and anti-CZP antibodies (predose)

Change #93

Section 8.7, bullet 27:

- CZP plasma concentrations and anti-CZP antibodies (following Protocol Amendment 8, these samples will no longer be collected)

Has been changed to:

- CZP plasma concentrations (for study participants enrolled following Protocol Amendment 9 only
- Anti-CZP antibodies (for study participants enrolled following Protocol Amendment 9 only)

Change #94

Section 8.8, bullet 11:

- CZP plasma concentrations and anti-CZP antibodies (following Protocol Amendment 8, these samples will no longer be collected)

Has been changed to:

- CZP plasma concentrations (for study participants enrolled following Protocol Amendment 9 only)
- Anti-CZP antibodies (for study participants enrolled following Protocol Amendment 9 only)

Change #95

Section 9, the following paragraph has been deleted:

Following Protocol Amendment 8, blood samples for determination of CZP plasma concentrations and anti-CZP antibodies will not be collected throughout the remainder of the study.

Change #96

Section 9, paragraph 1, the following sentence has been added:

For study participants enrolled prior to Protocol Amendment 9, samples for CZP plasma concentration and anti-CZP antibodies will no longer be collected.

Change #97

Section 9, paragraph 3, has been deleted:

For subjects already enrolled and treated prior to the implementation of Protocol Amendment 4 and hence undergoing a reduction of their dose, additional PK samples will be collected prior to dosing at the visit the dose change occurs and at the next 3 site visits following the dose change, ie, additional PK samples will be collected at either Unscheduled Visits or regular visits if not already planned per regular schedule. Afterwards, the regular PK sampling schedule applies.

Change #98

Section 9, paragraph 5, 6, 7, and 8, have been deleted:

Plasma concentration data for CZP from this study will be compared with plasma concentrations observed previously in adult subjects with RA, as described in Section 13.7. This plasma concentration analysis will be done on an ongoing basis throughout the study, starting when 6 subjects in 1 of the age groups have completed Week 12 (Visit 7).

Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future analyses indicate that plasma concentrations are outside of the exposure range of those observed in previous studies with adults, the dosing algorithm may be changed via a protocol amendment, and if necessary additional interim analyses including PopPK, may be performed. This study will continue during the PK analysis. All subjects assessed in this analysis will continue treatment after Week 12 (Visit 7).

Results of an interim PopPK analysis conducted in Jun 2013 suggest that while observed CZP plasma concentrations have remained in the adult range, they have been at the upper end of the distribution. Simulations predict that for some subjects in RA0043 receiving the originally determined loading doses up to Week 4 (Visit 5), plasma concentrations are likely to exceed the range previously seen in adult subjects receiving CZP 400mg Q2W. Furthermore, plasma concentrations of subjects receiving the originally determined maintenance dose after Week 4 (Visit 5) are predicted to exceed the concentration range observed in adults receiving CZP 200mg Q2W. Based on these findings, the dosing regimen will be changed with Protocol Amendments 4 and 5, and the doses to be administered will be

reduced by 50% for all weight groups. This dose change is intended to achieve plasma concentrations that are similar to the effective concentrations observed in previous studies in adult subjects with RA. Continued analysis of CZP plasma concentrations (including additional assessments for subjects undergoing a dose reduction with Protocol Amendment 4) will be performed to confirm that the 50% dose reduction will result in plasma concentrations within the target range of those observed in adults.

The final pediatric PopPK model will be combined with PD data (PedACR) and if the data allow, an exposure-response relationship will be derived.

Change #99

Section 9, paragraph 9, sentence 1:

Blood samples to determine plasma concentrations of CZP and anti-CZP antibodies will be analyzed by the central laboratory.

Has been changed to:

Blood samples to determine plasma concentrations of CZP and anti-CZP antibodies will be analyzed by a specialty laboratory.

Change #100

Section 9, paragraph 9, the following text has been added:

All study participants enrolled following Protocol Amendment 9 will have plasma concentrations of CZP and anti-CZP antibodies analyzed using an ECLIA method that meets current regulatory standards. In addition, PK and ADA samples (for which sufficient volume is available) collected in this study prior to Protocol Amendment 9 will be analyzed with the ECLIA method. The collective ECLIA-based PK data for this study will form the basis of any future CZP modeling and simulation work.

Change #101

Section 10.1.6 (Reporting requirements for events relating to TB) was added.

Change #102

Section 10.1.7, paragraph 1, sentence 2:

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

- The subject should return for an Early Discontinuation Visit. If pregnancy is determined at a study visit, the subject is withdrawn from the study and all Early Discontinuation Visit assessments should be completed at that visit.
- The subject should immediately stop receiving the IMP at the first confirmation of the pregnancy but no later than as instructed at the Early Discontinuation Visit.
- A Final Visit should be scheduled 12 weeks after the subject has discontinued their IMP..

Has been changed to:

Study medication must be discontinued as soon as pregnancy is known (by positive pregnancy test). Study participants can remain in the study under observation and should attend to scheduled visits regularly as their condition allows.

Change #103

Section 10.3, heading:

AEs of interest

Has been changed to:

AEs of special interest

Change #104

Section 10.3, paragraph 1, sentence 1:

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

Has been changed to:

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

Change #105

Section 10.3, paragraph 2:

Adverse events of interest include:

Has been changed to:

Adverse events of special interest include:

Change #106

Section 10.3, paragraph 2, the following text has been added:

- Potential Hy's Law

Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.

Change #107

Section 10.5, Table 10-1:

Preferred Term
Juvenile arthritis

Has been changed to:

Preferred Term
Juvenile idiopathic arthritis

Change #108

Section 10.6, paragraph 1, sentence 1:

Hematology, biochemistry, and urinalysis samples will be collected at Screening, Baseline, Weeks 4, 8, 12, 16, 20, 24, 32, every 8 weeks thereafter (every 16 weeks following Protocol Amendment 8), the Early Discontinuation/End of Treatment Visit, and the Final Visit 12 weeks after the last dose of study medication.

Has been changed to:

Hematology, biochemistry, and urinalysis samples will be collected at Screening, Baseline, Weeks 4, 8, 12, 16, 20, 24, 32 and every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8), the Early Discontinuation/End of Treatment Visit, and the Final Visit 12 weeks after the last dose of study medication. At Week 1, only CRP and PK samples will be collected and at Week 2, only CRP samples will be collected. In addition, hematology, biochemistry, and CRP samples will be collected at Unscheduled Visits for study participants undergoing a dose change (Section 7.2.1 and Section 8.6.1).

Change #109

Section 10.6, paragraph 1, sentence 3:

In addition, hematology, biochemistry, and CRP samples will be collected at Unscheduled Visits related to the dose change implemented with Protocol Amendment 4.

Has been changed to:

In addition, hematology, biochemistry, and CRP samples will be collected at Unscheduled Visits for study participants undergoing a dose change (Section 7.2.1 and Section 8.6.1).

Change #110

Section 10.6, paragraph 9:

If IGRA testing is required to be performed by the central lab (for all subjects from 5 to 17 years of age, see Section 6.2) additional blood sampling of approximately 3mL will be required at Screening.

Has been changed to:

The TB assessment by IGRA testing is required to be performed by the central lab; additional blood sampling of approximately 3mL will be required at Screening.

Change #111

Section 10.6, paragraph 10:

If the result of the IGRA is indeterminate, the test may be repeated once. The retest must be conducted in the allowable Screening window. Subjects with IGRA (performed ≤3 months prior to Screening) positive or indeterminate and a chest x-ray confirmative of TB infection are excluded (see Section 10.7.9.2).

Has been changed to:

If the result of the IGRA test is indeterminate, the test may be repeated once. If positive or indeterminate on retest, the study participant must not be enrolled (Section 10.7.9.5).

Change #112

Section 10.6, paragraph 11 and 12

For subjects from 2 to 4 years of age, PPD testing will be performed locally (except for subjects with documented BCG vaccination) as described in Section 10.7.9.2.4.

During the study and upon implementation of Protocol Amendment 7, IGRA testing should be done once a year (approximately every 48 weeks) for all subjects from 5 to 17 years of age. For subjects from 2 to 4 years of age, both IGRA and PPD testing should be performed once a year (approximately every 48 weeks). In cases where written documentation of BCG vaccination is available or previous PPD test was positive, only IGRA should be performed.

Has been changed to:

For study participants from 2 to 4 years of age, TST and IGRA testing will be performed (except for study participants with documented BCG vaccination) as described in Section 10.7.9.8.2. In countries with high BCG vaccination or high TST positivity, only IGRA should be performed (Section 10.7.9.8.2). The TST may be positive due to BCG vaccination, however, UCB will not permit enrollment of pediatric study participants <5 years old into the study with written approval from a physician with expertise in pediatric TB. IGRA testing should be done once a year (approximately every 48 weeks) for all study participants.

Change #113

Section 10.6, Table 10-2:

Hepatitis screening[c]
HBcAb HBsAb HBsAg HCVAb HBV DNA, if applicable
TB screening[d]
IGRA, PPD

Has been changed to:

Hepatitis screening[c]
HBcAb HBsAb HBsAg HCVAb HBV DNA, if applicable HCV RNA, if applicable
TB screening[d]
IGRA, TST
HIV Screening
HIV antigen or antibody

Change #114

Section 10.6, Table 10-2, footnote C:

Subjects will be tested for hepatitis at Screening. HBV DNA is required for subjects with only positive HBcAb (negative HBsAg and HBsAb) or only positive HBsAg. A hepatitis panel result which indicates immunity due to hepatitis B vaccination is not considered an exclusion criterion.

Has been changed to:

At Screening, laboratory testing includes testing for hepatitis B core antibody, hepatitis B surface antibody, hepatitis B surface antigen, hepatitis C virus antibody, and HIV 1/2. Study participants with a positive HBV test will not be allowed in the study (except for anti-hepatitis B positive only, in case study participant is immune due to well-documented

hepatitis B vaccination or isolated false-positive anti-HBc test confirmed with a confirmatory test such as hepatitis B virus deoxyribonucleic acid [HBV-DNA]). A positive hepatitis C antibody test will be confirmed by a confirmatory test (such as HCV RNA) and those with a positive confirmatory test will not be allowed in the study.

Change #115

Section 10.7.2, paragraph 1, sentence 1:

Height will be recorded at Screening, Baseline, every 24 weeks thereafter (every 48 weeks following Protocol Amendment 8), and the Early Discontinuation/End of Treatment Visit.

Has been changed to:

Height will be recorded at Screening, Baseline, every 24 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, the height assessment will be performed every 48 weeks following Protocol Amendment 8), and the Early Discontinuation/End of Treatment Visit.

Change #116

Section 10.7.3, sentence 2:

These assessments will be performed at Baseline, every 24 weeks thereafter, and the Early Discontinuation/End of Treatment Visit. Following Protocol Amendment 8, the assessments will be performed every 48 weeks, and only for subjects who have not reached Tanner stage V.

Has been changed to:

These assessments will be performed at Baseline and every 24 weeks thereafter, and the Early Discontinuation/End of Treatment Visit. For study participants enrolled prior to Protocol Amendment 9, Tanner stages assessment will be performed every 48 weeks following Protocol Amendment 8, and only for those subjects who have not reached Tanner stage V.

Change #117

Section 10.7.6, sentence 2:

If the subject is of reproductive potential and is sexually active, the method of birth control used will be recorded. Sexually active subjects (male and female) must use adequate contraceptive measures (see Section 6.2, Exclusion Criterion 17).

Has been changed to:

If the study participant is of reproductive potential and is sexually active, the method of birth control used will be recorded. Sexually active study participants (male and female) must use effective contraceptive measures (see Section 6.2, Exclusion Criterion 17).

Change #118

Section 10.7.9, heading:

Tuberculosis guidance, testing, and screening

Has been changed to:

Assessment and management of TB and TB risk factors

Change #119

Section 10.7.9, the following text has been added:

As TNF inhibitors are known to be associated with significant risk of reactivation of LTBI or previously treated active TB, appropriate rigorous precautions are being taken within the protocol (see Section 6.2 [Exclusion Criterion 11] and Section 6.4 [Withdrawal Criterion 2]).

Study participants with known active TB disease, at high risk of acquiring TB infection, or with past or current LTBI or current or history of NTMB infection are excluded from the study.

a. Known TB infection whether present or past is defined as:

- Active TB infection or clinical signs and symptoms strongly suggestive of TB (pulmonary or extra pulmonary).
- History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection.
- Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the participant 's medical history.

b. High risk of acquiring TB infection is defined as:

- Known close exposure (eg, sleeping in the same room) to another person with active TB infection within 3 months prior to Screening.
- Time spent within 3 months prior to Screening in a healthcare delivery setting or institution where individuals infected with TB are housed or where the risk of transmission of infection is high.

c. LTBI is defined as an infection by mycobacteria tuberculosis with:

- A positive IGRA (or 2 indeterminate IGRAs), AND
- Chest imaging (or other imaging) negative for TB infection, AND
- Absence of signs, symptoms (eg, evidence of organ-specific involvement), or physical findings suggestive of TB infection.

d. Pulmonary NTMB infection is defined as a group of lung infections caused by mycobacteria different from mycobacterium tuberculosis infections.

Change #120

Section 10.7.9.1, Section 10.7.9.2, Section 10.7.9.3 have been removed

Change #121

Section 10.7.9.1, Section 10.7.9.2, Section 10.7.9.3, Section 10.7.9.4, Section 10.7.9.5, Section 10.7.9.6, Section 10.7.9.7 have been added.

Change #122

Section 11.1, last paragraph:

Documentation of the assessment of all 6 core set measures will be submitted to UCB or designee for immediate review of completeness at Week 0 (Baseline), Week 16, Week 24, and Week 56, while the subject is still on site.

Has been changed to:

Documentation of the assessment of all 6 core set measures will be submitted to UCB or designee for immediate review of completeness at Week 0 (Baseline) and Week 24, while the study participant is still on site.

Change #123

Section 11.2, last paragraph:

These assessments are completed at Screening, Baseline, and every visit (including Unscheduled Visits that are related to the dose change implemented with Protocol Amendment 4) through the Early Discontinuation/End of Treatment Visit.

Has been changed to:

These assessments are completed at Screening, Baseline, and every visit (including Unscheduled Visits that are related to dose change) through the Early Discontinuation/End of Treatment Visit.

Change #124

Section 11.4, paragraph 2:

The Physician's Global Assessment of Disease Activity (VAS) will be completed at Screening, Baseline, and every visit (including Unscheduled Visits that are related to the dose change implemented with Protocol Amendment 4) through the Early Discontinuation/End of Treatment Visit.

Has been changed to:

The Physician's Global Assessment of Disease Activity (VAS) will be completed at Screening, Baseline, and every visit (including Unscheduled Visits that are related to dose change) through the Early Discontinuation/End of Treatment Visit.

Change #125

Section 11.5, paragraph 3, sentence 2:

The CHAQ will be completed by the parents/caregivers at Screening, Baseline, and every visit (including Unscheduled Visits that are related to the dose change implemented with Protocol Amendment 4) through the Early Discontinuation/End of Treatment Visit..

Has been changed to:

The CHAQ will be completed by the parents/caregivers at Screening, Baseline, and every visit (including Unscheduled Visits that are related to dose change) through the Early Discontinuation/End of Treatment Visit.

Change #126

Section 11.7, paragraph 2, sentence 2:

The Parent's Global Assessment of Overall Well-Being (VAS) will be completed at Screening, Baseline, and every visit (including Unscheduled Visits that are related to the dose change implemented with Protocol Amendment 4) through the Early Discontinuation/End of Treatment Visit.

Has been changed to:

The Parent's Global Assessment of Overall Well-Being (VAS) will be completed at Screening, Baseline, and every visit (including Unscheduled Visits that are related to dose change) through the Early Discontinuation/End of Treatment Visit.

Change #127

Section 11.8, sentence 2:

Samples will be collected at Screening, Baseline, and every visit (including Unscheduled Visits that are related to the dose change implemented with Protocol Amendment 4) through the Early Discontinuation/End of Treatment Visit.

Has been changed to:

Samples will be collected at Screening, Baseline, and every visit (including Unscheduled Visits that are related to dose change) through the Early Discontinuation/End of Treatment Visit.

Change #128

Section 11.10, last paragraph, last sentence:

Subjects not maintaining persistent CID following achievement of CRM and resuming treatment will restart the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a maintenance dose administered Q2W for the duration of the study, with exception of the lowest weight group, who will receive the maintenance dose Q4W following implementation of Protocol Amendment 4.

Has been changed to:

Study participants not maintaining persistent CID following achievement of CRM and resuming treatment will restart the fixed-dose CZP dosing based on their current weight with 3 loading doses of CZP administered Q2W over 6 weeks, followed by a maintenance dose administered Q2W for the duration of the study, with exception of the lowest weight group on the reduced dose regimen, who will receive the maintenance dose Q4W.

Change #129

Section 11.12, last paragraph, second sentence:

The FPS-R will be administered at Baseline and then daily during the first week of the study; at Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter (every 16 weeks following Protocol Amendment 8) through the Early Discontinuation/End of Treatment Visit.

Has been changed to:

The FPS-R will be administered at Baseline and then daily during the first week of the study; at Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) through the Early Discontinuation/End of Treatment Visit.

Change #130

Section 11.13, second paragraph, second sentence:

The Pain (VAS) will be completed at Baseline (acute and standard versions), daily during the first week of treatment (acute version); Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter (every 16 weeks following Protocol Amendment 8) through the Early Discontinuation/End of Treatment Visit (standard version).

Has been changed to:

The Pain (VAS) will be completed at Baseline (acute and standard versions), daily during the first week of treatment (acute version); Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) through the Early Discontinuation/End of Treatment Visit (standard version).

Change #131

Section 11.14, fourth paragraph, second sentence:

The Fatigue Assessment Scale will be assessed at Baseline, Weeks 1, 2, 4, 8, 16, 24, 32, then every 8 weeks thereafter (every 16 weeks following Protocol Amendment 8), and the Early Discontinuation/End of Treatment Visit. Preferably, the same parent/caregiver should complete the scale for each visit.

Has been changed to:

The Fatigue Assessment Scale will be assessed at Baseline, Weeks 1, 2, 4, 8, and then every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) and the Early Discontinuation/End of Treatment Visit.

Change #132

Section 12.4, the following text has been added:

A futility analysis of the PedACR30 response rate was performed after all active study participants on the reduced CZP dose had completed the Week 16 (Visit 8) assessments. If less than 50% of the study population enrolled on the reduced CZP dose regimen (Protocol Amendment 5) achieved a PedACR30 response at Week 16, the study was to be discontinued. The futility analysis confirmed that ≥50% of the study population enrolled on the reduced CZP dose regimen achieved a PedACR30 response at Week 16. A further futility analysis will not be performed using the additional participants that will be enrolled on the original CZP dose regimen following the implementation of Protocol Amendment 9.

Change #133

Section 13.2.1, paragraph 1, bullet 2:

Reduced CZP dose regimen: includes all subjects in the SS who began treatment in accordance with the reduced dosing regimen defined for the study (3 loading doses of CZP at Weeks 0, 2, and 4 [minimum=50mg Q2W, maximum=200mg Q2W] followed by a maintenance dose for the duration of the study [minimum=50mg Q4W, maximum=100mg Q2W]).

Has been changed to:

Reduced CZP dose regimen: includes all study participants in the SS who began treatment in accordance with the reduced dosing regimen defined for the study (3 loading doses of CZP at Weeks 0, 2, and 4 [minimum=50mg Q2W, maximum=200mg Q2W] followed by a maintenance dose for the duration of the study [minimum=50mg Q4W, maximum=100mg Q2W]). This subgroup includes all study participants who began the study with this CZP dose regimen and received 1 or more doses of this regimen, regardless of any subsequent switch to the original CZP dose regimen.

Change #134

Section 13.2.2:

Approximately 55 centers are planned to enroll 156 subjects into this study. The enrollment per site is limited to a maximum of 12 subjects.

Has been changed to:

Approximately 55 centers are planned to enroll the original 156 study participants into this study. A subset of these centers will be used to enroll the additional 30 study participants following Protocol Amendment 9. The enrollment per site is limited to a maximum of 12 study participants.

Change #135

Section 13.3, paragraph 1, sentence 1:

The incidence of AEs will be assessed as primary safety variable in this study.

Has been changed to:

The incidence of serious TEAEs and TEAEs leading to permanent withdrawal of IMP will be assessed as primary safety variables in this study. Other safety variables include the incidence of TEAEs, TEAEs of interest, TEAEs by relatedness, TEAEs by severity, and TEAEs by duration of exposure.

Change #136

Section 13.3, paragraph 4, sentence 1 and 2:

For the original CZP dose regimen subgroup, in addition to the overall presentation of AEs, AEs will be summarized separately for the periods of exposure to original and reduced CZP dose regimens. Additionally, the frequency and percentage of AEs reported during the first 16 weeks of study medication exposure will be summarized separately for the 2 CZP dose regimens (original CZP dose regimen, reduced CZP dose regimen).

Has been changed to:

For the original CZP dose regimen subgroup, in addition to the overall presentation of AEs, AEs will be summarized separately for the periods of exposure to original CZP dose regimen and the reduced CZP dose regimen, in addition to exposure for study participants that switched from the reduced CZP dose regimen to the original CZP dose regimen following Protocol Amendment 9.

Change #137

Section 13.4, paragraph 1:

Certolizumab pegol plasma concentrations and anti-CZP antibody concentrations will be assessed as primary variables in this study.

Has been changed to:

Certolizumab pegol plasma concentrations levels at Week 16 and Week 48 will be assessed as primary variables in this study. Other PK and immunological variables include CZP plasma concentrations at other study timepoints and anti-CZP antibody levels throughout the study.

Change #138

Section 13.4, paragraph 2:

Plasma concentrations will be used to build a PopPK model with the nonlinear mixed-effect modeling (NONMEM) software.

Has been changed to:

Plasma CZP concentrations will be used to build a PopPK model with the nonlinear mixed-effect modeling (NONMEM) software. The model will be parameterized in terms of clearance, volume of distribution, and absorption rate constant. Details of the PopPK modeling procedures will be described in a separate data analysis plan. The pediatric PopPK model will be combined with PD data (PedACR) and if the data allow, an exposure response relationship will be derived. These modeling analyses and results will be reported separately.

Change #139

Section 13.4, paragraph 3, 4, 5, 6, and 7:

A meta-analysis was previously performed by adding the pediatric data to the adult data in a PopPK analysis within NONMEM (C87068 and CL0153) for the Week 24 interim analysis (with ELISA data).

For the final analysis, UCB will be re-assaying all available PK samples (ie, for which sufficient volume is available) with a newly developed MSD bioanalytical assay. The data from the re-assayed RA0043 PK samples will be used to build a PopPK model.

The model will be parameterized in terms of clearance, volume of distribution, and absorption rate constant. Details of the PopPK modeling procedures will be described in a separate data analysis plan. Analyses and results will be reported in a separate report.

The pediatric PopPK model will be combined with PD data (PedACR) and if the data allow, an exposure-response relationship will be derived.

Individual anti-CZP antibody concentrations will be listed and the incidence of anti-CZP positive (>2.4units/mL) subjects will be summarized by study visit and overall incidence by Baseline age stratum (all subjects, 2 to 5 years, 6 to 11 years, and 12 to 17 years). In addition safety and efficacy profiles by antibody status will be investigated.

Certolizumab pegol plasma concentration data will be tabulated and summarized by dose regimen (original CZP dose regimen or reduced CZP dose regimen) for each visit on which samples were taken (geometric mean, arithmetic mean, minimum, maximum, standard deviation and % coefficient of variation). Plasma concentration time curves will be plotted separately for subjects who began treatment according to the original CZP dose regimen or the reduced CZP dose regimen, overall, by Baseline age stratum, and by anti-CZP antibody status. Subgroup analyses will include an analysis of the subjects enrolled and treated up to the Week 16 timepoint under the original maintenance dosing regimen.

Has been changed to:

All study participants enrolled following Protocol Amendment 9 will have plasma CZP concentrations and anti-CZP antibodies analyzed using the ECLIA method. In addition, PK and ADA samples (for which sufficient volume is available) collected in this study prior to Protocol Amendment 9 will be analyzed with the ECLIA method.

Data from the ECLIA method will constitute the study's main PK and anti-CZP antibody evaluations. As such, PK and anti-CZP antibody data generated with the original ELSIA method will be reported as Listings. Plasma CZP concentration data generated by the ECLIA method will be tabulated and summarized (geometric mean, arithmetic mean, minimum, maximum, standard deviation and % coefficient of variation) by study dose regimen (original CZP dose regimen or reduced CZP dose regimen) for each PK sampling visit. Plasma concentration time curves will be plotted, along with respective individual anti-CZP antibody titers where available, separately for study participants who began treatment according to the original CZP dose regimen or the reduced CZP dose regimen, overall, and by Baseline age stratum. Subgroup analyses will include study participants enrolled with Protocol Amendment 9 and those treated up to the Week 16 timepoint under the original maintenance

dosing regimen. Where available, individual ECLIA-based anti-CZP antibody data will be tabulated by study visit and Baseline age stratum (all study participants, 2 to 5 years, 6 to 11 years, and 12 to 17 years). In addition, safety and efficacy profiles by antibody titers (or titer categories) may be investigated.

Change #140

Section 13.5, paragraph 5, bullets 14 and 15:

- Change from Baseline on FPS-R (child-reported, for subjects ages 5 to 11 years), daily during the first 7 days of treatment; Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit. Following Protocol Amendment 8, change from Baseline on FPS-R is assessed every 16 weeks.
- Change from Baseline in JIA Pain VAS, daily during the first week of the study (acute and standard versions); Weeks 4, 12, 16, and 24; and then every 8 weeks thereafter through the Early Discontinuation/End of Treatment Visit (standard version) for subjects ages 12 to 17 years. Following Protocol Amendment 8, change from Baseline in JIA Pain VAS is assessed every 16 weeks.

Has been changed to:

- Change from Baseline on FPS-R (child-reported, for study participants ages 5 to 11 years), daily during the first 7 days of treatment; Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) through the Early Discontinuation/End of Treatment Visit.
- Change from Baseline in JIA Pain VAS, daily during the first week of the study (acute and standard versions); Weeks 4, 12, 16, 24, and then every 8 weeks thereafter (for study participants enrolled prior to Protocol Amendment 9, visit frequency changes to every 16 weeks instead of every 8 weeks following implementation of Protocol Amendment 8) through the Early Discontinuation/End of Treatment Visit (standard version) for study participants ages 12 to 17 years.

Change #141

Section 13.7, the following text was added:

A futility analysis of the PedACR30 response rate was performed after all active study participants enrolled on the reduced CZP dose had completed the Week 16 (Visit 8) assessments. If less than 50% of the study population enrolled on the reduced CZP dose regimen (Protocol Amendment 5) achieved a PedACR30 response at Week 16, the study was to be discontinued. The futility analysis confirmed that ≥50% of the study population enrolled on the reduced CZP dose regimen achieved a PedACR30 response at Week 16. Given the descriptive nature of the data presentations, there were no statistical implications of this interim analysis. A further futility analysis will not be performed using the additional subjects that will be enrolled on the original CZP dose regimen following the implementation of Protocol Amendment 9.

In addition to the futility analysis, several interim analyses were planned, including interim analyses of PK data, and full interim analyses of PK, immunogenicity, safety, and efficacy endpoints, as described below.

Change #142

Section 13.7, paragraph 1 and 2, the following text was removed:

Interim analysis of PK data will compare CZP plasma concentration data from this study with CZP plasma concentrations observed previously in adult subjects with RA. Interim analysis of CZP plasma concentrations was started when 6 subjects in 1 of the age groups completed Week 12 (Visit 7).

Comparisons will be made between the Week 12 geometric mean and median values for the pediatric and adult subjects, as well as between the individual pediatric data and the adult 5th and 95th percentile and minimum and maximum observed values.

Change #143

Section 13.7, paragraph 3:

If the pediatric plasma concentrations demonstrate that the geometric mean and median concentrations are below the adult 5th percentile or above the 95th percentile, the PK data will be used to re-evaluate the weight-based dose adjustment algorithm for pediatric subjects. Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future interim analyses, which may include PopPK, indicate that plasma concentrations of JIA subjects are outside of the exposure range observed in previous adult RA studies, a revised pediatric dose algorithm will be derived. Any change in dose regimen will require a protocol amendment prior to implementation.

Based on results of an interim PopPK analysis conducted in Jun 2013 described in Section 5.1, the dosing regimen will be changed with Protocol Amendments 4 and 5, and the doses to be administered will be reduced by 50% for all weight groups. This change is intended to achieve plasma concentrations similar to the effective concentrations observed in previous studies in adult subjects with RA.

Has been changed to:

Per original protocol, if the pediatric plasma concentrations demonstrate that the geometric mean and median concentrations are below the adult 5th percentile or above the 95th percentile, the PK data will be used to re-evaluate the weight-based dose adjustment algorithm for pediatric study participants. Interim CZP plasma concentration data available at the time of Protocol Amendment 3 indicated that no change to the dosing algorithm was required. The protocol stated that if future interim analyses, which may include PopPK, indicate that plasma concentrations of JIA study participants are outside of the exposure range observed in previous adult RA studies, a revised pediatric dose algorithm will be derived. Any change in dose regimen will require a protocol amendment prior to implementation.

An interim analysis of PK data conducted following Protocol Amendment 3 compared CZP plasma concentration data from this study with CZP plasma concentrations observed previously in adult study participants with RA. Interim analysis of CZP plasma concentrations was started when 6 study participants in 1 of the age groups completed Week 12 (Visit 7). Comparisons were made between the Week 12 geometric mean and median values for the pediatric and adult study participants, as well as between the individual pediatric data and the adult 5th and 95th percentile and minimum and maximum observed values.

Based on results of this interim PopPK analysis (also described in Section 5.1), the dosing regimen was changed with Protocol Amendments 4 and 5, and the doses to be administered were reduced by 50% for all weight groups. This change was intended to achieve plasma concentrations similar to the effective concentrations observed in previous studies in adult study participants with RA.

Change #144

Section 13.7, paragraph 5, 6, 7:

For the Week 24 interim clinical study report, the CZP plasma concentrations were monitored following the change in dose regimen to confirm they were within the targeted adult range. Following Protocol Amendment 8, no more interim PK analyses will be performed, and the final PK data to be reported will use a new MSD assay, and consequently no further comparison will be performed with respect to the adult RA concentrations range.

After all active subjects have completed the Week 16 (Visit 8) assessments, an interim analysis of PedACR30 response rates will be performed and the study will be discontinued if less than 50% of the study population enrolled on the reduced CZP dose regimen (Protocol Amendment 5) achieves a PedACR30 response at Week 16. Given the descriptive nature of the data presentations, there are no statistical implications of this interim analysis.

After the last subject has reached the Week 24 Visit (Visit 10), the database will be cut and a full interim analysis of all safety and efficacy endpoints will be performed based upon 24 weeks of exposure for each individual (or all data for those cases who withdrew before this timepoint).

Has been changed to:

An interim analysis of PK, immunogenicity, safety, and efficacy endpoints was performed after all active study participants that were enrolled and treated prior to implementation of Protocol Amendment 9 had completed the Week 24 (Visit 10) assessments, and the results were reported separately. An interim analysis, including all enrolled participants, for all PK, immunogenicity, safety, and efficacy endpoints will be performed after all active study participants, including those enrolled following the implementation of Protocol Amendment 9, have completed the Week 24 (Visit 10) assessments.

Change #145

Section 13.8, paragraph 1:

Based upon the ICH guideline for the assessment of safety, it is planned to enroll a sufficient number of subjects to this study to have a minimum of 100 with at least 12 months continuous exposure to CZP. Assuming a dropout rate of approximately 20%, it was originally determined that 125 subjects would need to be enrolled. At the time of Protocol Amendment 5, 78 subjects had been enrolled according to the original CZP dose regimen, and it is planned to enroll a further 78 subjects on the reduced CZP dose regimen, so that a comparable number of subjects on the reduced CZP dose regimens can be analyzed. Thus, the total number of subjects planned to be enrolled will be increased to 156 subjects. Assuming a Screening failure rate of 25%, it is planned to screen 195 subjects in total.

Has been changed to:

Based upon the ICH guideline for the assessment of safety, it is planned to enroll a sufficient number of study participants to this study to have a minimum of 100 with at least 12 months continuous exposure to CZP. Assuming a dropout rate of approximately 20%, it was originally determined that 125 study participants would need to be enrolled. At the time of Protocol Amendment 5, 78 study participants had been enrolled according to the original CZP dose regimen, and it was planned to enroll a further 78 study participants on the reduced CZP dose regimen, so that a comparable number of study participants on the reduced CZP dose regimens could be analyzed. Thus, the total number of study participants planned to be enrolled was increased to 156 study participants. Assuming a Screening failure rate of 25%, it is planned to screen 195 study participants in total.

Change #146

Section 13.8, the following text has been added:

With Protocol Amendment 9, an additional 30 study participants will be enrolled on the original dose regimen with the aim to enroll at least 5 study participants in each weight range of 10 to <20kg (22 to <44lb), 20 to <40kg (44 to <88lb), and ≥40kg (≥88lb).

Change #147

Section 16, the following reference has been added:

FDA Guidance for Industry – Bioanalytical Method Validation. 2018.

18 DECLARATION AND SIGNATURE OF INVESTIGATOR

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

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

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

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

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

Investigator:

Printed Name	Date/Signature

19 SPONSOR DECLARATION

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

Approval Signatures

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Version: 1.0

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Title: RA0043 - Protocol Amendment 9 - Phase 3 - Open-label

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Document Approvals	
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